

3D-Printing for Radiotherapy Using Flexible Filament Materials

A thesis submitted to the University of Manchester for the degree
of Doctor of Clinical Science in the Faculty of Biology, Medicine
and Health

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Abstract

Use of 3D-printing within healthcare is well established due to its ability to re-create complex geometry at relatively low cost and in a fraction of the time taken to produce such designs through conventional subtractive manufacturing techniques. Despite this, interpretation of the legal requirements for medical devices, concerns surrounding biocompatibility of 3D-printed materials, as well as potentially complex software workflows, have restricted uptake and more widespread development in a radiotherapy setting. Following a literature review of 3D-printing in radiotherapy and production of a clinical 3D-printed brachytherapy surface applicator using a rigid thermo-plastic material, a demand and research need for flexible printer filament materials was identified.

Dosimetric and physical characterisation of two commercially available materials, NinjaFlex and Cheetah, was carried out in order to enable their use as photon bolus through assignment of an appropriate density override within the TPS. A clinical case study using 3D-printed flexible bolus to fill a nasal cavity of a patient undergoing radiotherapy treatment suggests it is an accurate, efficient and cost-effective method with the potential to improve treatment outcomes and patient experience.

With focus on use of low-cost 3D-printers and open-source or in-house software solutions, it is hoped this research can provide a foundation on which more widespread use of 3D-printing within radiotherapy can be realised. Future research will likely focus on the suitability of 3D-printed materials as medical devices, improving workflow and integration within a radiotherapy department and addressing the environmental concerns regarding use of thermoplastics.

Declaration

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Finally, I could not ask for a more supportive and loving partner. Thankyou Hannah for making this journey with me and for the unconditional support you have given me throughout.

Background to the Author

I studied Physics with Finance BSc at the University of Surrey, Guildford, U.K. during which, I undertook an industrial placement at the Institute Laue-Langevin in Grenoble, France. I graduated with honours in 2006. In 2007 I completed a medical physics MSc, also at the University of Surrey. In 2007 I began training as a clinical scientist at the University Hospital Birmingham, Birmingham, U.K. Following completion of the IPEM clinical scientist training scheme in 2011, I was awarded a DipIPEM and registered as a clinical scientist with the HCPC. Following registration as a clinical scientist I started work at the Mount Vernon Cancer Centre, Northwood, Middlesex, U.K. Here I worked as a clinical scientist and provided scientific advice and support to aspects of radiotherapy quality assurance, treatment planning and brachytherapy. In 2013 I was assigned a role as the department's lead imaging physicist where I hold responsibilities for the implementation and development of a widespread programme of image guided radiotherapy (IGRT) techniques. I maintain QA and treatment planning responsibilities and act as a medical physics expert (MPE) in this capacity. In 2015 I obtained a place on the higher specialist scientist training programme (HSST), a five-year workplace based training programme supported by a Doctoral level academic award. My main research interests are in development and optimisation of image verification techniques, adaptive treatment of urologic disease, in-vivo dosimetry and application of novel technologies, including the use of 3D-printing in radiotherapy.

Statement for the Examiners

This thesis is submitted for the degree of Doctor of Clinical Science. It aims to cover the research component (C2) carried out as part of the DClinSci degree programme. The DClinSci programme is a five-year doctoral level degree and forms the academic component of the HSST programme. Award of the degree is based not only on this work but also on satisfactory completion of an innovation project (C1) and two taught components: leadership & management (section A) and medical physics (section B). For the taught components, a total of 21 assignments have been completed with an approximate total word count of 50,000 as well as four assessed presentations. The innovation project was assessed via a written innovation proposal, a literature review and a lay presentation. Commencement of the programme was in November 2015 with work on the innovation and research work starting in 2017/2018. The degree was delivered on a part-time basis with students notionally allocated one day a week outside of normal workplace duties wherever possible. Taught components were delivered via face-to-face teaching at both the University of Manchester and the University of Liverpool. A summary of all additional work carried out in support of this degree is given in Appendix 1. The innovation proposal developed as part of the innovation project is included as Appendix 2 and formed a major contributing factor to the decision to pursue 3D-printing as a research topic.

Rationale for Submission as Journal Format

This thesis is being submitted in journal format due to the nature in which the research has been conducted, as individual case studies, designed to complement existing clinical practice. It is anticipated that each of the three papers presented as part of this work provide individual contribution to the existing literature and that collectively they describe the journey taken from concept to clinical implementation.

Abbreviations

ABS	Acrylonitrile Butadiene Styrene
AMBS	Alliance Manchester Business School
CBCT	Cone Beam Computed Tomography
CT	Computed Tomography
FDM	Fused Deposition Modelling
GTV	Gross Tumour Volume
HDR	High Dose Rate
HSST	Higher Specialist Scientist Training
IMRT	Intensity Modulated Radiotherapy
MRI	Magnetic Resonance Imaging
MV	Megavoltage
PC-ISO	Polycarbonate-International Standards Organisation
PDD	Percentage Depth Dose
PEI	Polyetherimide
PLA	Polylactic Acid
PTV	Planning Target Volume
QA	Quality Assurance
SLS	Selective Laser Sintering
SSD	Source to Surface Distance
STL	Stereolithography
TMR	Tissue Maximum Ratio
TPS	Treatment Planning System
VMAT	Volumetric Modulated Arc Therapy

Chapter 1 - Introduction

1.1 Background to the Research

At the Mount Vernon Cancer Centre, mould room resource has been in steady decline over the preceding few years and there is a limited number of staff with sufficient technical expertise to efficiently produce custom made bolus using commercial materials. Commercially available sheet bolus is used more commonly where offered, but this does not contour well to particularly complex surface geometries and can be costly if not being reused. Re-use of bolus carries a potential infection risk to the patient and is not encouraged. 3D-printing was identified as a potential solution to the manufacture of highly complex shaped bolus. With the majority of the manufacturing process automated, 3D-printing offers the potential for a significant amount of staff time to be saved. It was also envisaged that 3D-printing could be utilised in various other ways throughout the department such as in the production of dosimetry phantoms and equipment, spare parts and brachytherapy applicators. A business case and innovation proposal were prepared in support of a charitable bid for the LulzBot Taz 6 3D-printer (Aleph Objects Inc. Colorado, U.S.A.). The innovation proposal considered use of 3D-printing for custom bolus and brachytherapy applicators and recommended it as an innovative and practical way to address problems

with existing manufacturing techniques. A number of potential barriers to implementation were initially identified, including use of open-source or commercially expensive software options, legal issues and the classification of 3D-printed objects as medical devices, and a steep learning curve with a potentially lengthy commissioning process. The complete innovation proposal is available as Appendix 2. The printer was purchased in 2017 and commissioned for manufacture of clinical bolus using rigid plastic filament materials in 2018. Using flexible bolus in place of rigid plastics had always been a priority but a lack of existing research and the technical challenges it presented, necessitated further research of our own and followed a sustained period of education and familiarisation. In view of initial successes and in support of this research, a 3D-printing in radiotherapy clinical study day was held at the Mount Vernon Cancer Centre in September 2019. The course was initiated and organised by the author to share experiences and inspire further developments. The day was attended by approximately forty delegates and was backed by three major sponsors. An agenda detailing the presented content is available as Appendix 3.

1.2 3D-printing

Three-dimensional (3D) printing is a form of additive manufacturing whereby a 3D object may be formed layer by layer from a range of materials,

notably, but not limited to, plastic [1]. The primary advantage of additive manufacturing is its ability to create almost any complex shape or geometric feature at a fraction of the time taken to produce such designs through conventional subtractive manufacturing techniques. 3D objects may be generated through image acquisition (CT, MRI, photogrammetry) and/or with the aid of Computer-Assisted Design (CAD) software [2].

Within healthcare, 3D-printing has been applied since the early 2000s when it was first used to make dental implants and custom prosthesis [3]. Currently it is used to produce a wide variety of prostheses, implants and anatomical models for surgical planning [4]. Potential future trends include bioprinting of complex organs and repair of external organs such as the skin [5].

The benefits of 3D-printing within the wider healthcare sector have encouraged investigation into the use of 3D-printing within radiotherapy and undoubtedly there are techniques to which its versatility can improve accuracy, efficiency, convenience, and ultimately patient outcomes.

There are several different methods of 3D-printing with the most commonly encountered being Stereolithography (SLA), Selective Laser Sintering (SLS) and Fused Deposition Modelling (FDM) [6].

With SLA printers, objects are created through selective curing of liquid polymer resin layer-by-layer using light of specific wavelength. SLS printing utilises high powered lasers to selectively sinter small particles of polymer

powder, fusing them together layer-by-layer into a single solid structure. SLS printing uses thermoplastic polymers supplied in a granular form. SLA and SLS printers are typically able to print with a higher layer resolution and accuracy but are significant in cost when compared to FDM and are therefore less popular. FDM printing typically works by heating and extruding thermoplastic filament from a moveable nozzle onto a heated glass bed. A schematic representation of the major components of a typical FDM printer is shown in Figure 1.

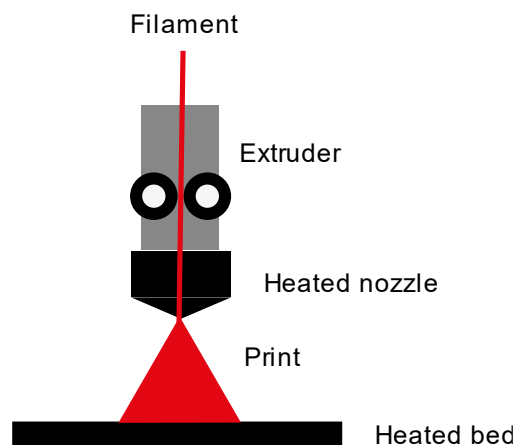


Figure 1 Schematic representation of a typical FDM style printer

Unlike SLA and SLS, FDM printers offer the ability to print at varying infill rates but are typically slow, and complex shapes may require the addition of support material to avoid prints failing. A summary of 3D-printing techniques is shown in Table 1 [2].

Method	Advantages	Disadvantages
Stereolithography (SLA)	Large part size, good accuracy	Moderate Strength
Selective Laser Sintering (SLS)	Large part size, variety of materials, good strength and accuracy	High cost, powdery surface
Fused Deposition Modelling (FDM)	Low Cost, good strength	Low Speed

Table 1 Overview of three popular 3D-printing techniques [2]

Although capable of using exotic materials such as wood and metal composites, FDM printing typically uses thermoplastics and the most widely used being Acrylonitrile Butadiene Styrene (ABS) and Polylactic Acid (PLA). For radiotherapy use, suitable materials should be similar to water in radiation attenuation and scatter properties, biocompatible and sterilisable (for in-vivo use) and free of CT scanning artefacts [7]. Various studies have investigated the dosimetric, biological and physical characteristics of each and a summary of their advantages and disadvantages is shown in Table 2 [8] [9] [10].

Material	Advantages	Disadvantages
Acrylonitrile Butadiene Styrene (ABS)	Electron density similar to water	Prone to layer separation, warps easily [8] [9]
Polylactic Acid (PLA)	Low failure rate [9]	High electron density

Table 2 An overview of ABS and PLA printer materials

With FDA-approved biocompatibility, Polycarbonate-ISO or PC-ISO (Stratysys, Eden Prairie, MN) has been suggested as an alternative to ABS and PLA for temporary implants in the body [11] [12]. Although printers capable of printing in PC-ISO are prohibitively expensive at present, a more viable option may be to outsource the printing process to an external provider [11]. Soft, rubber like materials such as TangoPlus are available, have the potential to minimise patient discomfort and have been shown to be tissue equivalent at typical brachytherapy energies [13] [14] [15].

1.2.1. The LulzBot Taz 6

Throughout this work, 3D-printing has been carried out solely using the LulzBot TAZ 6 3D-printer [16], Figure 2. The TAZ 6 is an FDM-style printer with an integrated automatic bed levelling system, all metal hot-end, heated polyetherimide (PEI) surface and a relatively large build volume of 280 mm × 280 mm × 250 mm. The printer is entirely open source, both hardware and software may be freely copied, modified and converted.



Figure 2 The LulzBot TAZ 6 3D-printer [16]

The original tool head of the printer was replaced with the FlexyDually (Version 2) (Aleph Objects Inc. Colorado, U.S.A.), shown in Figure 3. The FlexyDually consists of dual extruders capable of printing at temperatures of up to 300°C with the rear extruder designed specifically for use with flexible filaments.



Figure 3 The LulzBot TAZ FlexyDually (Version 2) tool head [16]

Additional modifications were made to the printer to improve cooling of the stepper motors using heat sinks and the print area was enclosed using Perspex in an attempt to reduce warping. Additionally, the printer was interfaced to the hospital network using a Raspberry Pi (Raspberry Pi Foundation, Cambridge, U.K.) and the open-source OctoPrint software (<http://www.octoprint.org>). This configuration allowed the printer to be remotely monitored and controlled, vastly improving the efficiency of the printing process as less time was spent travelling to and from the printer to examine progress. Additionally, uploading of print instructions (G-code) could be done from virtually anywhere within the hospital. A relatively slow process of manufacture, prints are often left to run unattended for several hours. Excess noise and potentially toxic fumes necessitated careful

consideration to where the printer was located. Existing mould room facilities were used as they benefitted from air extraction and minimal occupancy.

1.2.2. Slicing and G-code

3D-printers are supplied instruction via G-code. Conversion of a 3D object to G-code is performed using slicing software (slicer). A variety of commercial and open-source slicing software exists. Cura, slicing software created by David Braam is open source and available under the LGPLv3 licence. Developed by Ultimaker, it is currently the world's most popular 3D-printing software [17]. It is also the recommended slicing software for use with the TAZ 6 printer which is distributed with its own custom LulzBot edition. A wide range of print settings can be configured within Cura and the process of achieving optimal parameters for a specific printer and filament material can be overwhelming. LulzBot issue complete lists of print settings for a range of filaments used in combination with their printers via print profiles that may be imported into Cura. These default print profiles may form the basis for further modification and optimisation. Changes to printer settings can have a significant effect on print quality and can lead to changes to the dosimetric properties of the printed materials. Commissioned print profiles can be a useful way of ensuring print settings are maintained and are

consistent with time. Care should be taken when making changes to printer profiles, especially following the completion of any commissioning process.

A summary of some of the most influential slicer settings is given in Table 3.

Setting	Description	Typical range	Effects
Layer height	Specifies the height of each filaments layer, analogous to resolution. Prints made with thinner layers are smoother and more detailed.	0.1-0.4 mm	Print quality, speed
Shell thickness	Defines the thickness of the outside shell of the print.	0.4-0.8 mm	Strength
Retraction	Retracts the filament when the nozzle is moving over a non-printed area. Prevents excess filament oozing from the nozzle producing stringy, poor quality prints.	Enabled/Disabled	Print quality
Fill density/Infill	How densely filled the inside of the print will be. The higher the percentage the stronger and heavier the printed object will be.	20-80%	Strength, material cost, speed
Print speed	Speed at which the extruder travels while it produces filament. Slower speeds typically yield higher quality prints. Specific to material type.	10-100 mm/s	Print quality, speed
Printing temperature	Temperature of the hot end, varies for different material types.	210°C (PLA) - 240°C (NinjaFlex)	Print quality
Supports	Whether or not to print additional sacrificial structures used to support areas of significant overhang.	Enabled/Disabled	Print quality, speed, material cost

Platform adhesion type	Options to prevent corners of prints lifting from the build platform due to warping. A raft creates a horizontal grid underneath the object, a brim adds an additional single layer around the object. Both are removed afterwards.	Raft/Brim/Disabled	Bed adhesion, speed, material cost
Bed temperature	The temperature of the heated print bed (when available). Slows down cooling of the initial layers to prevent warping.	40°C-80°C	Bed adhesion
Initial layer thickness	Thickness of the very first layer on the print bed. Helps to produce strong prints and maintain good adhesion of the print to the bed.	0.3-0.6 mm	Bed adhesion, strength

Table 3 Summary of some of the most influential slicer settings

1.2.3. Infill Rate and Pattern

Of all the available printer settings, the infill percentage has the greatest potential to alter the dosimetric properties of printed objects. The infill or fill density describes how densely filled the inside of the printed object will be. High infill percentage corresponds to high density and high homogeneity; zero infill percentage corresponds to a hollow print. Various patterns of infill also exist, with the most commonly encountered being rectangular, triangular, wiggle and honeycomb. Infill pattern and percentage are typically chosen as a compromise between strength and speed, with

prototypes printed at low infill rates and a fast printing pattern such as rectangular. Final production prints may be made using high infill rates and strong patterns such as triangular. A schematic representation of some typical infill rates and patterns is shown in Figure 4.

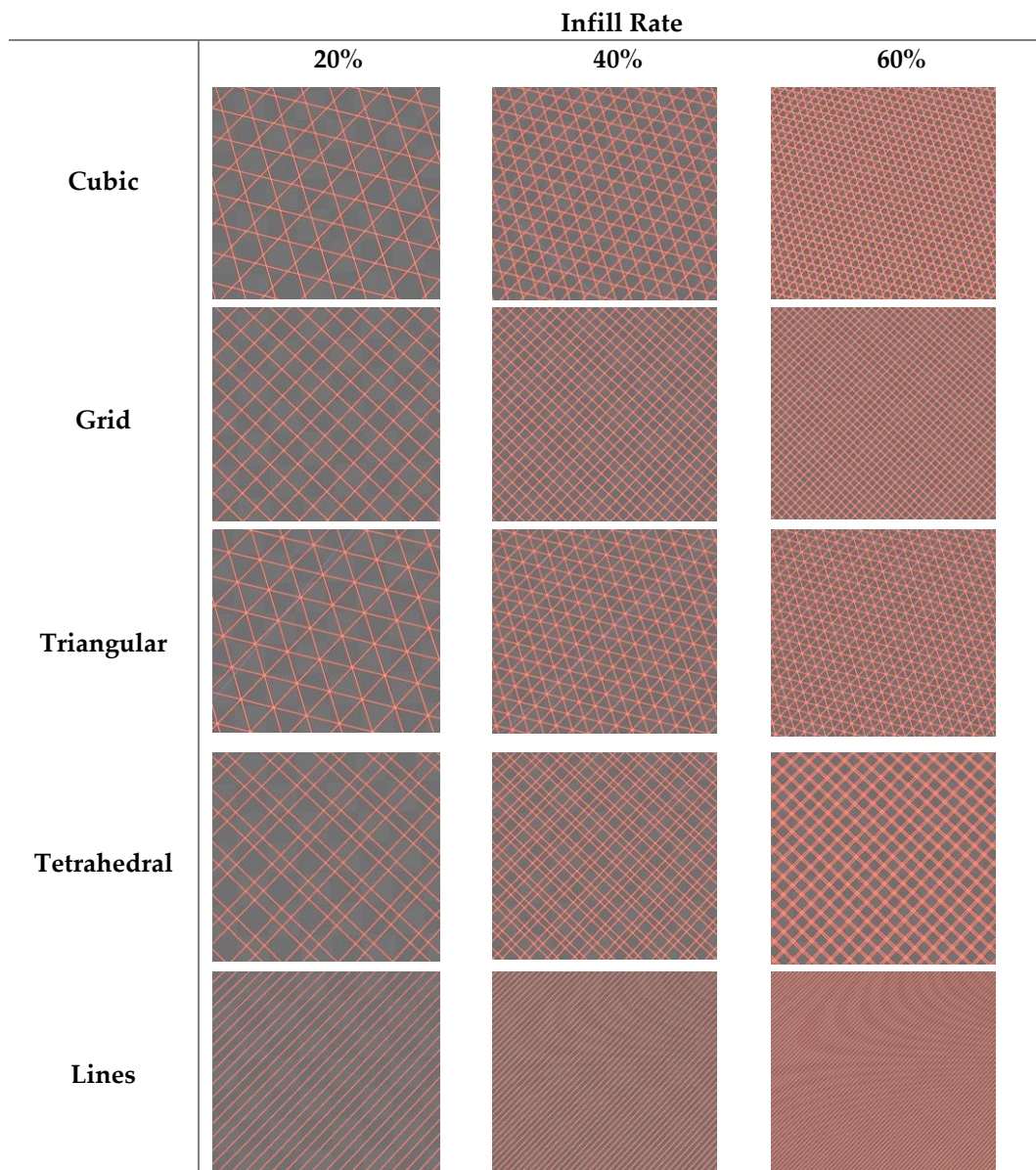


Figure 4 Schematic representation of common infill rates and patterns taken from the Cura slicing software [17]

1.3 Radiotherapy

In the U.K. around one in three people are diagnosed with cancer and around half of them will receive radiotherapy as part of their course of treatment [18]. Radiotherapy utilises ionising radiation targeted to a

particular treatment volume and normally delivered over a course of treatment fractions spanning several weeks. High energy (>1 MeV) radiotherapy is particularly well suited to delivering radiation doses to deep situated tissues due to the fact that the relative dose to the skin is lower than it is at depth. When treating at or near the skin surface, this skin-sparing effect is less advantageous and alternative methods using low energy x-rays, electrons or brachytherapy sources may be preferential. Alternatively, tissue mimicking materials or bolus may be applied to the skin to alter the dose received at depth and on the skin surface. Bolus material may also be used to compensate for missing tissue or for irregular tissue shapes to enable more predictable, consistent and accurate calculation and delivery of radiotherapy treatment plans. Treatments that typically require use of bolus include those which involve the skin. These can be benign, i.e. mycosis fungoides or shallow seated malignant tumours such as those found within the head and neck region.

1.3.1. Bolus

Radiotherapy bolus is typically produced from square, flat sheets of commercially available material such as Superflab [19], see Figure 5. Alternatively, thin sheets of dental wax may be built up in layers directly

upon a patient surrogate, usually a thermoplastic mould or plaster impression.



Figure 5 Superflab commercially available bolus material [19]

These materials are well established within radiotherapy and are relatively effective for the majority of treatment sites. For highly irregular surfaces, such as those found on the nose or within the ear, use of two dimensional 'flat' bolus to conform to three-dimensional contour change can be challenging and resulting air gaps potentially detrimental to treatment outcomes.

1.3.2. Brachytherapy

Brachytherapy is a form of radiotherapy delivered using sealed radioactive sources placed inside or adjacent to, a treatment area. It is an excellent option

in the treatment of small superficial lesions, providing a fast dose fall-off helping to protect nearby clinical structures [20]. Brachytherapy is typically delivered using a small ^{192}Ir line source welded to the end of a flexible drive cable which can be extended via a series of channels which are normally connected to applicators or catheters placed on or within the patient.

1.3.3. Surface Applicators

Surface brachytherapy is delivered using skin applicators or surface moulds. Similar to radiotherapy bolus, brachytherapy surface applicators are designed to fit closely to a patient's skin surface and are typically made from water equivalent materials to aid dosimetric calculation. Additionally, they consist of small hollow guides through which the flexible drive cable and radioactive source may transition. Here they can be positioned for a pre-determined time in order to achieve a satisfactory planned dose distribution. Commercially available surface applicators include the Freiburg Flap (Elekta, Stockholm, Sweden) and Mick (Mick Radio-Nuclear Instruments, Inc.) applicators. Fundamentally these consist of a two-dimensional flexible mesh of silicone rubber pads with evenly space, integrated, flexible catheters. Alternatively, three-dimensional surface moulds can be manufactured using flexible catheters fitted to a thermoplastic patient impression with wax or similar used to provide sufficient standoff and backscatter.

1.4 Research Hypothesis and Objectives

3D-printing presents a potential alternative to conventional means of manufacture of custom-made devices in radiotherapy such as tissue bolus and brachytherapy applicators. As a relatively new technology, it is anticipated that its benefits to radiotherapy are not yet fully realised and that more widespread implementation has been limited due to expense, technical challenges, gaps in the research and the legal implications and uncertainties surrounding use of custom medical devices.

This thesis aims to better understand and address some of these challenges and to investigate the technical challenges surrounding use of novel flexible filament materials through a series of clinical case studies. The research hypothesis is therefore described as:

“The advantages of 3D-printing to radiotherapy are not yet fully realised. Using low-cost, FDM style 3D-printers combined with flexible filament materials can result in the efficient production of accurate and comfortable custom-made devices which will ultimately help improve patient experience and treatment.”

The primary objectives of the thesis have been identified as:

- Research and review existing use of 3D-printing in radiotherapy
- Identify barriers and enablers to more widespread clinical implementation
- Detail use of 3D-printing using low cost FDM style printers for production of patient specific devices
- Investigate dosimetric properties of flexible filament materials
- Detail clinical implementation of bolus using flexible filament materials

Secondary objectives to be considered:

- Explore use of custom made and open-source software to facilitate the design and production of custom-made radiotherapy devices
- Explore medico-legal issues surrounding use of 3D-printed devices for radiotherapy, including issues of biocompatibility and interpretation of the relevant regulations governing use of medical devices

Chapter 2 – Literature Review

An initial review of 3D-printing in radiotherapy was carried out to identify gaps in the existing research and any potential barriers to implementation of clinical techniques. The review is presented here, adapted from that written for publication in the Journal of Applied Clinical Medical Physics (JACMP) in 2020. Several key areas were identified in the literature where 3D-printing was being considered or applied to techniques within radiotherapy. Very little evidence of clinical implementation was seen and reasons for this include a lack of detailed understanding of printed materials, interpretation of the relevant legislation, and overly complex software workflows. The vast majority of existing studies cover use of rigid plastic printed materials. Flexible printing materials exist, may be advantageous to the patient and better replicate the bolus materials 3D-printing is likely to replace. Further characterisation of flexible filament materials as well as documented clinical case studies were identified as key enablers to this exciting technology and form the basis for the work presented in this thesis.

2.1 Existing Reviews

Several reviews of 3D-printing in medicine refer to radiotherapy.

Furthermore, several reviews of 3D-printed materials in the context of

radiotherapy exist and are summarised in this review. In their review of 3D-printing based on imaging data, Rengier et al. reference 3D-printing in radiotherapy as a helpful tool for rapid prototyping [2]. Pugh et al. reviewed 3D-printing within radiotherapy as means to improve bolus conformity whilst acknowledging its potential use for patient immobilisation [21]. Despite evidence that current practice of bolus fabrication is limited by time, resources and accuracy and with 3D-printing being widely promoted as a viable alternative, there are few reports to date of the use of 3D-printing for actual patient treatment [22]. Pugh et al. highlight several advantages of using 3D-printed bolus including a reduction in production time, decrease in cost and improved patient experience but advise that implementation requires establishment of vigorous QA procedures to ensure patient safety and geometrical accuracy [21]. Other limitations identified by their review include restricted print volumes, extended production times and the long term stability and dosimetric properties of currently available 3D-printer materials such as ABS and PLA [21] [23].

A review of a selection of patient cases in one centre highlights the versatility of 3D-printing in clinical radiation oncology including its use in the production of custom photon bolus and brachytherapy surface applicators [22].

Bio-printing has been identified as an emerging technology; whereby tissue equivalent materials may be printed directly within a structure. This has the potential to allow production of immobilisation devices complete with tissue equivalent bolus, reducing uncertainties due to air gaps during delivery of VMAT techniques [21]. With a potential bias from vendors producing 3D-printers, caution is advised when deciding what fabrication device and material to use.

2.2 Search Strategy

Review and reporting was guided by the PRISMA statement [24]. A literature review of PubMed and Google Scholar was conducted using the search criteria of: ('3D' OR 'three-dimensional' OR '3D-Printed') AND 'print*' AND ('radiotherapy' OR 'radiation therapy'), limited to articles published within the last ten years, relevant to radiotherapy in humans only and published in the English language. This initial search criteria returned 139 results which were subsequently reviewed by the author and selected and categorised based upon the satisfying criteria. Key papers identified in

the references were also reviewed to ensure all relevant literature were included. A total of 58 articles were identified and analysed for this study, the process of identification and selection in accordance with PRISMA is detailed further in Figure 6. Results were categorised according to one of six categories depending on the theme of their research. The resulting categorisation is shown in Table 4. A summary of all the literature used in this review, listed according to their categorisation, is given in Appendix 4.

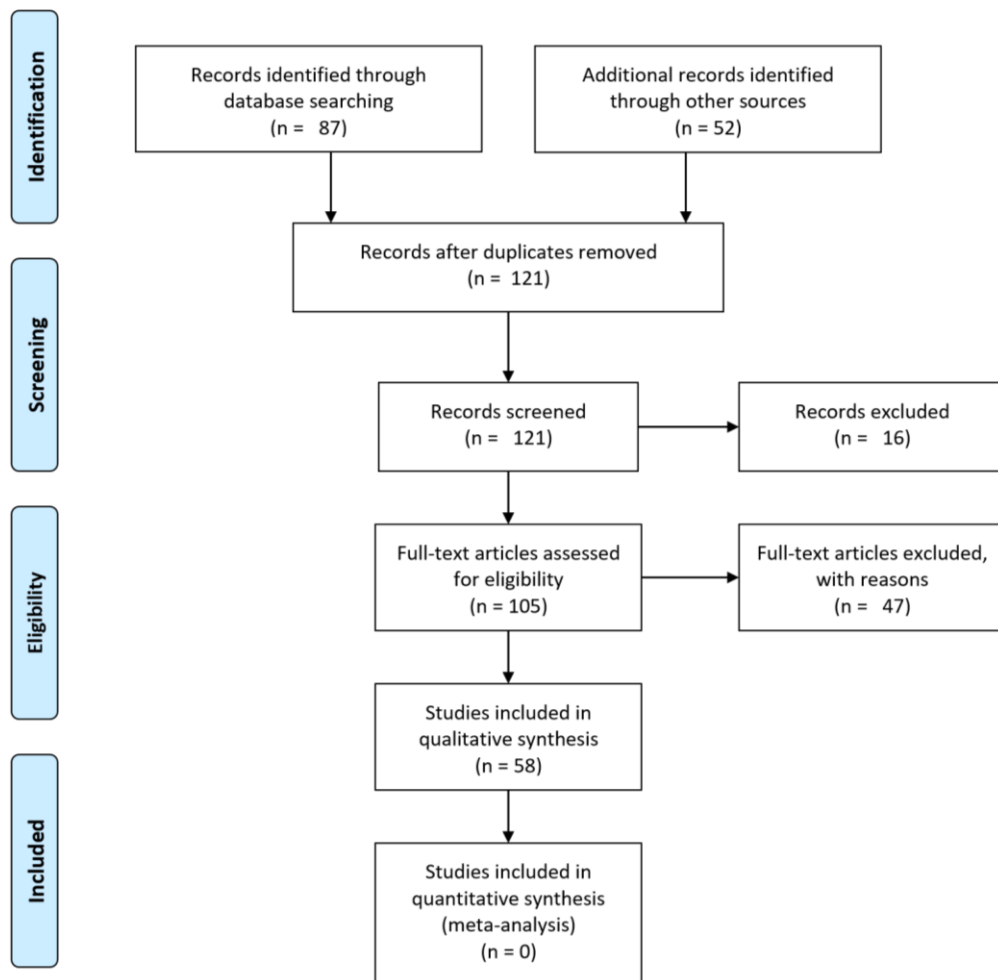


Figure 6 PRISMA [24] Flow diagram of the review process

Category	Number of Articles
Review	4
Immobilisation Devices	6
Brachytherapy	14
Bolus Materials	16
Phantom Design	14
Other Uses	4
Total	58

Table 4 Categorisation of articles included in this study

2.3 Techniques

Research into techniques using 3D-printing were categorised into one of five headings: phantom design, immobilisation, bolus material, brachytherapy or other.

Phantom Design

Within radiotherapy, solid phantoms are typically used when performing dosimetry measurements in order to validate treatment planning system algorithms for commissioning, quality assurance and clinical research.

Commercially available phantoms can be expensive and limited in geometry and physical properties [25]. In contrast, 3D-printed phantoms have the potential to be a viable, low cost and highly customisable alternative [26] [27] [28]. Complex 3D-printed phantom designs have been proposed for verifying

motion tracking systems [29] [27], dose algorithms [30], radiotherapy treatment couches [31] and image registration [32].

For validation of individual patient treatment plans, typically conducted for complex radiotherapy techniques such as IMRT and VMAT, patient specific dosimetry measurements may be performed. These are typically carried out using standard shape phantoms which bear little resemblance to the patient and potentially mask dosimetric errors caused by complex patient anatomy [9]. In order to expand the clinical usefulness of these measurements, patient-specific phantoms have been proposed based on 3D models produced from a planning CT scan [9] [33] [34] [35]. Such methods would allow for a complete end-to-end assessment of treatment, taking account of effects of the treatment couch and any immobilisation devices. They can however be slow to manufacture and accuracy limited by print homogeneity and segmentation of the patient surface from any overlaying structures. Creation of heterogeneous density phantoms that can provide bulk density matches of bone, lung and soft tissues would be advantageous. 3D-printed variable density phantoms have been produced of comparable uniformity to that of commercially available low-density lung phantoms [25] [36]. Further work towards the production of heterogeneous phantoms is proposed [33] [34]. Due to their large size and physical density, 3D-printing entire phantoms can be significantly time consuming and efforts have been made to reduce print

time using 3D-printed shells filled with tissue equivalent materials [33].

Despite this, further refinement of the phantom construction process is sought and remains a limiting factor prior to implementation into a clinical workflow [9] [35].

Immobilisation

Immobilisation is used widely within radiotherapy in attempt to maintain geometrical accuracy and reproducibility during and throughout treatment.

Immobilisation typically utilises thermoplastic materials directly moulded to patient anatomy or alternatively to a pre-prepared plaster positive. This process can be distressing for the patient and the resulting moulds do not always provide a good fit [37]. Using image data from both CT and MRI datasets it is possible to segment anatomical data and produce geometrically accurate 3D-printed treatment shells comparable to those found using currently adopted techniques [37]. However, using CT data alone, Fisher et al. found discernible differences between a planned shell and physical realisation, potentially due to inaccurate segmentation of the skin surface [38]. Subcutaneous tissue is not well defined by CT images and MRI would be better suited to this task, although at the expense of increased geometric uncertainty due to motion blurring and distortion [37]. A study by Haefner et al. demonstrated the feasibility of using MRI to produce 3D immobilisation

masks amongst a group of healthy volunteers [39]. A similar method using diagnostic CT has been suggested to allow symptomatic and frail patients to avoid additional imaging and mask moulding sessions in preparation for whole brain radiotherapy [40]. MRI may not be routinely available to most radiotherapy departments and alternative approaches such as use of laser scanning or photogrammetry may yet prove to be a viable alternative at relatively low cost [38] [41] [42].

Technology variations across 3D-printer vendors and proprietary infill patterns may result in unknown radiological properties for use in radiotherapy; a method of commissioning is detailed by Meyer et al. [43].

Dosimetric properties of a range of 3D-printed materials, at thicknesses up to 4 mm, have been found to be comparable to currently used commercial thermoplastics, with one study reporting a maximum attenuation of 1% for a 6 MV photon beam [37].

A cost comparison suggested 3D-printed shells may be more expensive to produce than conventional soft drape masks when using commercially available printing services but with the cost of 3D-printers reducing this difference will become less significant as increasingly departments are acquiring their own printing equipment [37].

No evidence of clinical implementation of 3D-printing for patient immobilisation purposes was found in the literature although ethical approval for a prospective clinical comparison with conventional radiotherapy treatment shells has been discussed [37].

Bolus

One of the most widespread application of 3D-printing within radiotherapy to date has been in the production of patient specific bolus used to increase surface dose for treatments to the skin, eyes or other superficially located disease. In total sixteen articles were found with eleven related to photon treatments, five to electron treatments. Conventional methods of bolus production for complex patient geometries is a challenging and highly labour-intensive process; 3D-printing may offer greater efficiency [44] [45], with reduced operational and production costs [46].

Material Considerations

The challenge with production of any bolus is in the production of tissue mimicking materials that can be accurately matched to complex surface irregularities. Thermoplastic materials are widely used for this purpose and both ABS and PLA have been found to exhibit good agreement to water with respect to both their physical and electron densities through measurements of Percentage Depth Dose (PDD) and Tissue Maximum Ratio (TMR) [46].

ABS is most closely matched to water but may be more prone to integrity compromises.

Using FDM techniques, the density of 3D-printed objects may be varied by adjustments to the infill percentage, which, dependent on infill pattern, exhibits an approximately linear relationship [47]. With so many combinations of infill pattern and type, it is suggested that each should be investigated [46]. Studies to date utilise linear or rectilinear patterns with between 80-100% infill with good results [46] [47]. It is likely that optimal parameter settings for 3D bolus printing has not yet been realised [48].

In order to account for irregularities in equivalence of the bolus materials, use of a specific Hounsfield Unit (HU) assignment within the TPS is crucial [46]. This helps to ensure accurate modelling within the TPS and may be obtained through CT scanning of the material [49] [50] or through empirical means based on best matching to measured results [46] [51]. Meyer et al. have detailed a framework for clinical commissioning of 3D-printed patient devices [43].

For electron treatments, where positional shifts in the depth of dose maximum of up to 8 mm for 12 MeV has been observed, it may be necessary to adjust the thickness of the 3D-printed bolus to account for this and potentially limit the occurrence of severe skin erythema [46].

Bolus materials inevitably come into direct contact with a patient's skin and biocompatibility of printed materials must be considered and used in accordance with relevant medical device laws and legislation. With few clinical examples and potential confusion surrounding classification of 3D-printed bolus as a medical device, plastic wrap has been used in an attempt to maintain sanitary conditions [46].

Geometrical Considerations

Accurate geometrical production of bolus is crucial in order to maintain good fit to a patient surface. This can be difficult to achieve with commercially produced flat-form bolus which can reduce both the dose coverage and dose homogeneity in the target volume [48] [52]. 3D-printed bolus has been shown to provide good surface fit to a variety of complex geometries [52] [53]. Comparison with custom bolus produced using paraffin gauze suggests 3D-printed bolus can provide a more precise reconstruction of a reference bolus with greater homogeneity [54]. Although pre-clinical studies suggest reproduction accuracy less than 1 mm, in one particular clinical study a maximum difference between the planned and the printed bolus was 5 mm [55]. In a separate clinical study of sixteen patients treated intermittently with 3D-printed bolus, at least one had problems with fitting, suggesting that more vigorous QA may be required [53]. QA of 3D-prints can be time

consuming and current methods potentially impractical on an individual patient basis [46].

Although usefully serving to limit intra-fraction movement, rigid plastics such as PLA or ABS do not easily allow for patient changes during treatment such as weight changes and inflammation. Bolus made using these materials may therefore need occasional redesign and reproduction, potentially adding considerable time to the treatment process [45]. Adding a margin of 1-2 mm may be useful to accommodate for such uncertainties and can ease placement of the bolus in situ [14]. Alternatively flexible, malleable materials may be used and can help lessen any discomfort found during treatment at the expense of increased cost and print time [14].

Brachytherapy

Brachytherapy is an effective radiotherapy treatment for certain internal tumour types and superficial diseases, particularly those with irregular, multi-curved surfaces to which the effect of electron treatment can be limited. Brachytherapy is typically delivered using standard applicators or custom-made surface moulds designed to provide good match to patient anatomy. Poor applicator or surface mould fitting can significantly increase dose uncertainty and the use of 3D-printing has been proposed to produce

custom made applicators for gynaecological tumours [6] [11] [50] [55] [57] and surface moulds for skin applicators [51] [15] [13] [58] [59].

Custom printed gynaecological applicators may be advantageous particularly to patients with non-standard anatomy such as those with narrow vaginal vaults [56] [7] where a desired applicator shape may be produced based on physical examination [12]. More accurate models may be produced through designs based on imaging, incorporating either real time or post-processed expansion of the relaxed vaginal cavity [12]. One proposed method involves the delineation of contrast-soaked vaginal gauze [60].

Applicator templates have also been developed as guides for commercially available vaginal applicators, allowing individualised oblique needle tracks whilst avoiding contact between 3D-printed parts and radioactive sources, mitigating the need for an accurate internal patient model [56] [7]. A clinical study of two patients treated using 3D-printed, personalised vaginal templates showed potential, providing there is easy access to local printing facilities and further studies are sought in order to shift design and manufacturer from a manual to a semi-automatic or automatic process [57].

3D-printed templates for guidance of radioactive seed implantation has been clinically implemented [61] [62]. One study in a cohort of fourteen patients suggested good accuracy following comparison of pre and post-operative

plans [62]. Another study observed the clinical effects of use of 3D-printed templates for treatment of recurrent malignant head and neck tumours [63]. Surface mould skin applicators are typically fabricated manually using wax, built up in layers with integrated applicator guides. The process may be both time consuming and challenging, requiring skilled technical staff. 3D-printing may offer a more convenient and cost effective way to produce surface mould applicators for various sites [64] including the hands [13], breast [59] and the face [58]. A financially focused study into the use of 3D scanning and printing for non-melanoma skin cancer brachytherapy, found a 34% reduction in time required to fabricate a treatment mould and an associated 49.5% reduction in financial cost due to the lack of need for an additional CT scan and subsequent production of a patient impression required to make a traditional mould [58]. Removing the requirement for an impression greatly improves the patient experience and, with a relatively automated manufacturing process, can increase efficiency, particularly for those departments with limited experience of mould room practice or limited mould room resources [15].

Other

Other potential uses for 3D-printing in radiotherapy found in the literature were in the fabrication of Cerrobend® grids for spatially modulated therapy

(grid therapy), as part of a novel method to deliver passive-scattering proton beams with a fixed range and modulation for stereotactic radiosurgery [65] [66] and as a novel method to design and manufacture oral stents from CT images used during radiotherapy [67]. 3D-printed bolus material has also been suggested as a potential proton compensator [68] [69] and to help fabricate Cerrobend® compensators for total body irradiation [70]. For head and neck radiotherapy, oral stents may help reduce detrimental treatment effects. Using 3D-printed stents can help increase access to such devices at those centres without dental and oral/maxillofacial facilities and local specialists [67].

2.4 Discussion

Despite being developed over 30 years ago, 3D-printing still continues to make headline news with recent reports of 3D-printed food, bridges and prosthetic arms, suggesting it is making a valuable contribution to society [71]. Relatively recent implementation within a radiotherapy setting makes it difficult to conclude whether 3D-printing applied in this way is here to stay or simply a technology fad. Nonetheless, 3D-printing offers a novel solution to many of its challenges and offers the potential for low-cost bespoke adaption of treatments provided the remaining research barriers can be overcome.

Barriers to Implementation

Although this review has highlighted several examples of 3D-printing with strong evidence of advantage over current radiotherapy practices, implementation within a clinical setting appears to be slow. Despite significant developments over the last ten years, affordable (sub £1,000) 3D-printers are still limited in size, capability and print speed. Coupled with a steep learning curve, 3D-printing techniques can have significant adverse impact upon the workload of a typical radiotherapy department [21]. For successful widespread clinical implementation of 3D-printing within radiotherapy these factors, alongside research challenges of material characterisation and efficient workflow should first be addressed. Additionally, consideration for QA of 3D-printed objects should be made, especially important during the early stages where geometrical and physical reproduction may be uncertain.

Material Characteristics

Despite research into characterisation of the physical and dosimetric properties of the two main materials used in FDM printing (ABS and PLA), there has been no strong recommendation to use one material over the other. Detailed characterisation of exotic and more novel materials is lacking and questions remain over their long term stability of most materials following

radiation exposure [46]. A study of a range of materials by Craft et al. reported widespread variation in Hounsfield unit and density, even when printing using the same printer and material batch [23].

Further characterisation may be required particularly for specialist use in brachytherapy and kilovoltage radiotherapy. Lack of understanding and experience of use of 3D-printed materials and techniques within a medical setting can make interpretation of relevant legislation difficult. In the United States, guidance has been provided on the use of additive manufacturing for medical devices by the Food and Drug Administration (FDA) [72]. It would be prudent for regulatory bodies in the U.K. such as the Medicines and Healthcare Products Regulatory Agency (MHRA) to provide similar guidance in order to alleviate any concerns potential users may have.

Software Solutions and Clinical Workflow

Software solutions designed for 3D-printing of medical devices are few in number, can be prohibitively expensive and do not necessarily lend themselves well to the patient workflow within a typical radiotherapy department. One of the challenges of any such solution is the ability to accurately segment volumetric information from imaging data, a task that most radiotherapy treatment planning systems can already achieve [48].

There potentially exists an opportunity to significantly reduce both the cost

and complexity associated to this task through innovative use of the intrinsic abilities of the TPS. There is evidence in the literature of work to this effect through use of custom-built software and in-house scripting within the TPS itself. Further collaboration with the manufacturers of such applications could be sought and efforts made to better integrate the 3D-printing and treatment planning processes. As well as increasing ease of use, any improvement to workflow has the potential to reduce process errors which may otherwise yield poor geometry and failed prints.

Future Applications

Currently, the overwhelming advantages of 3D-printing in radiotherapy appears to be in the production of custom made bolus and brachytherapy treatment applicators due to an associated reduction in staff time and resources when compared to conventional manufacturing techniques [53]. However, it is likely that there remain applications not yet fully developed or even conceived. These may include the development of customised vaginal implants for brachytherapy and photogrammetry based techniques for surface volume rendering [33] [38]. Material developments could facilitate the production of tissue and organ mimicking phantoms, which, when coupled with printable inserts for radiation measuring devices, could allow

more complex quality assurance of individualised radiotherapy treatment plans.

2.5 Conclusion

This review highlighted several key areas where 3D-printing is currently in use or undergoing development within radiotherapy. In particular, 3D-printing offers a way to improve conformity and production efficiency of custom bolus and has the potential to replace traditional methods using commercially available materials. Further research into the characteristics of existing and novel 3D-printer materials may be of value. Improvement to the integration of 3D-printers within the radiotherapy environment must also be sought. Complex software often duplicates features available of conventional radiotherapy systems and can be expensive. With further development and increased clinical uptake, it is likely additional use of 3D-printing within radiotherapy will emerge. It may then become clearer whether 3D-printing is a genuinely innovative idea or a technology fad. The numerous positive studies presented here suggest the latter remains unlikely.

Chapter 3 - Empirical Papers

The following sections are presented as independent journal articles intended for peer-reviewed publication in the Journal of Applied Clinical Medical Physics and currently in the process of being submitted.

Following the literature review, identification of a lack of evidence of clinical implementation of 3D-printing in radiotherapy and a desire for increased flexibility of printed devices, compelled further investigation.

3.1 3D-printed Brachytherapy Surface Applicator

Whilst identifying flexible filament materials suitable for use with a recently acquired 3D-printer, an opportunity arose to investigate the feasibility of manufacturing 3D-printed brachytherapy applicators. Despite the comprehensive mould room facilities and clinical expertise available at the Mount Vernon Cancer Centre, it was anticipated and the literature demonstrated, that 3D-printing could be a viable, cost-effective alternative with potential to improve patient comfort, experience and treatment outcomes [64] [73]. The clinical experience was documented as a case study with additional consideration given towards the end of the research, to use of flexible filament materials.

3.1.1. Title and authors

The full title of the article contained within this sub-section is:

“Design and manufacture of 3D-printed brachytherapy surface applicators – a clinical case study for treatment of mycosis fungoides of the lower leg.”

The primary author of this article is James Burnley, with advice and contribution from Gerry Lowe, Peter Hoskin and Geoff Budgell.

3.1.2. Abstract

High dose rate brachytherapy is an effective form of treatment for diseases located at the surface of the skin, particularly for areas of high surface obliquity which may otherwise be difficult to treat using electrons or photons. Custom made surface applicators may be used during treatment to guide and position radioactive sources accurately and reproducibly and these are typically manufactured using wax layers built upon a thermoplastic shell. A custom applicator was designed using anatomical information available via a pre-treatment CT scan for a patient undergoing treatment for mycosis fungoides of the lower leg. The applicator was 3D-printed using a low-cost, FDM style printer at considerably less cost and time compared to a more conventional method of manufacturer, largely due to the absence of a mould room appointment. During treatment, the applicator was easy to

position and provided a good fit to the patient surface. Unlike its conventionally made alternative, the rigid plastic from which the applicator was printed, offered little flexibility to anatomical change. Flexible filament materials used in similar fashion may enable production of a more robust applicator design, these are discussed, and some initial results presented. Flexibility aside, given the difficulties manufacturing brachytherapy applicators, with limited resources and a lack of experience, 3D-printing offers an excellent, potentially automated alternative, regardless of the material used.

3.1.3. Introduction

High dose rate (HDR) brachytherapy can be an effective radiotherapy treatment technique, particularly for superficial lesions that present on surfaces with significant obliquity or in areas that may be difficult to treat with conventional radiotherapy such as the scalp, nose and limbs. HDR applicators are used to guide radioactive sources in close proximity to a particular treatment location where they remain for a calculated time period before being withdrawn. The steep dose fall-off provided by brachytherapy sources necessitates applicators that conform well to the treatment surface, that are stable during a treatment fraction and reproducible over a course of treatment. Commercially available applicators such as the Freidburg Flap

(Elekta, Stockholm, Sweden) are designed to be tailored to an individual patient but do not always adhere well to the skin [51]. Custom-made surface moulds may also be used but the manufacturing process can be labour-intensive and time-consuming and the precise placement of catheters within the mould can be challenging [51]. At the Mount Vernon Cancer Centre, surface moulds have traditionally been made using wax, built up in layers placed on the surface of a thermoplastic shell, with catheters inserted between the layers through which the HDR source may travel. The thermoplastic shell is contoured to the patient during an initial mould room appointment. This requires considerable resource and may not be well tolerated dependent on how sore or tender the intended treatment area is. With a potential lack of experience and expertise required to produce good quality, well fitting, custom-made surface moulds and dosimetric uncertainties associated with HDR, the use of external beam techniques such as volumetric-modulated arc therapy (VMAT) may be favoured [74]. 3D-printing has been established as a viable alternative for manufacturing custom-made bolus for external beam radiotherapy [46] [75]. Such bolus is also designed to conform to an individual patient skin surface, replacing commercially available wax-like materials that it would be otherwise difficult to achieve equivalent results with. It is possible that HDR applicators could be produced in a similar fashion by designing bolus based

on CT data but containing holes or channels in which a source may be positioned using a catheter as a guide. 3D-printing has been used previously within brachytherapy for this purpose [73] [64] as well as for manufacturing internal gynaecological applicators [57] [11] and grid templates for seed implants [61] [62]. Several feasibility studies have also been carried out to assess potential savings attributed to using 3D-printed surface applicators. One study reported a 34% reduction in fabrication time and 49.5% reduction in financial cost, in part due to the reduction in number of patient appointments and time on a CT scanner [58]. Removing the requirement for a lengthy and potentially invasive impression appointment, greatly improves the patient experience. A relatively automated manufacturing process, can increase efficiency, particularly for those departments with limited experience of mould room practice or limited mould room resource [73]. In this study, we present the clinical implementation of a 3D-printed, custom, brachytherapy surface applicator made using a low-cost, FDM style 3D-printer. The process of applicator design, manufacture and treatment planning is described for a clinical case of treatment to the leg for a patient with mycosis fungoides disease. The applicator was manufactured from acrylonitrile butadiene styrene (ABS). ABS is widely used for 3D-printing within radiotherapy due to its widespread availability, ease of use and the fact that its relative density is close to that of water. However, ABS is rigid at

room temperature and so offers little flexibility to changes in a patient's skin surface as can typically be expected over a course of, and in response to, treatment.

3.1.4. Materials and Method

Case Study

An 84-year old female diagnosed with mycosis fungoides was referred for palliative brachytherapy treatment to an area of the upper leg. Consideration was also made for treatment using electrons, however as the treatment area extended over approximately two-thirds of the leg's circumference, the resulting distal dose fall off would necessitate multiple matched radiation fields. This was deemed to be overly complex and at increased risk of geographical miss during treatment. The patient was prescribed 12 Gy to be delivered over a course of three fractions. The patient attended a pre-planning CT appointment and a CT scan was acquired using a Siemens Definition AS scanner (Siemens, Munich, Germany) with 2 mm slice thickness. A radio-opaque wire was used to help identify the treatment area which was subsequently contoured as a clinical tumour volume (CTV) in the BrachyVision™ (Varian Medical Systems, Inc, Palo Alto, CA) treatment planning system. The CTV extended approximately 12 cm in the sup-inf direction and 13 cm laterally. The CTV contour was expanded 1 cm laterally

to produce a planning target volume (PTV). A photograph of the CTV to be treated using brachytherapy, marked by radio-opaque wire is given in Figure 7.



Figure 7 Clinical tumour volume to be treated with brachytherapy (centre of image) the area of the lower leg (right of image) was to be treated separately using electrons

Applicator Design

The CTV was expanded by 2 cm in all directions and cropped from the skin with an additional 1 mm margin to allow for some positional uncertainty when applying the finished applicator to the patient. A distance of 2 cm was chosen as this allowed for sufficient stand-off of the source (normally 5 mm),

sufficient medium in which to secure the catheters in which the source could travel and a small amount of back scatter material. Additional back scatter could be added later either using conventional bolus materials or by means of an additional 3D-printed bolus. Larger expansions may be more desirable, negating the need for additional material and allowing for uncertainties in the initial CTV volume at the expense of increased print time and material costs. For significantly large applicators, consideration to patient comfort and tolerance must also be made. The initial applicator design was exported as a DICOM structure and an in house developed MATLAB (MathWorks, Cambridge, U.K.) script was used to create catheter trajectories at a specified stand-off and separation distance. Further details of the script and its associated functions are available as Appendix 5. Trajectories were smoothed using locally estimated scatterplot smoothing (LOESS). Individual trajectories could be manually added or removed, and the final configuration was exported as a series of three-dimensional cylinders 3 mm in diameter. Both the initial applicator design and the cylinder trajectories were subsequently imported to the open-source software, MeshMixer (Autodesk Inc. California, U.S.A.) and a Boolean operation was performed to effectively hollow out the cylinders from the applicator to create the internal guides for the catheters. MeshMixer's plane cut feature was then used to provide open ends in which to insert catheters as well as to produce a single flat edge

which could be used to maximise adhesion of the print to the print bed. The smooth tool was used to further smooth the inside edge of the applicator to improve patient comfort. At this stage, using the tools available in MeshMixer, additional scatter material could easily be added. In practice however, we found it to be preferential to add it at the time of treatment and used SuperFlab (Mick Radio-Nuclear Instruments Inc., Mount Vernon, NY), a commercially available bolus material. Three designs were produced using varying amount of stand-off, 8 mm, 12 mm and 16 mm, with the 16 mm design used for the final print following results of an initial mock plan. A simplified schematic of the design workflow is shown in Figure 8.

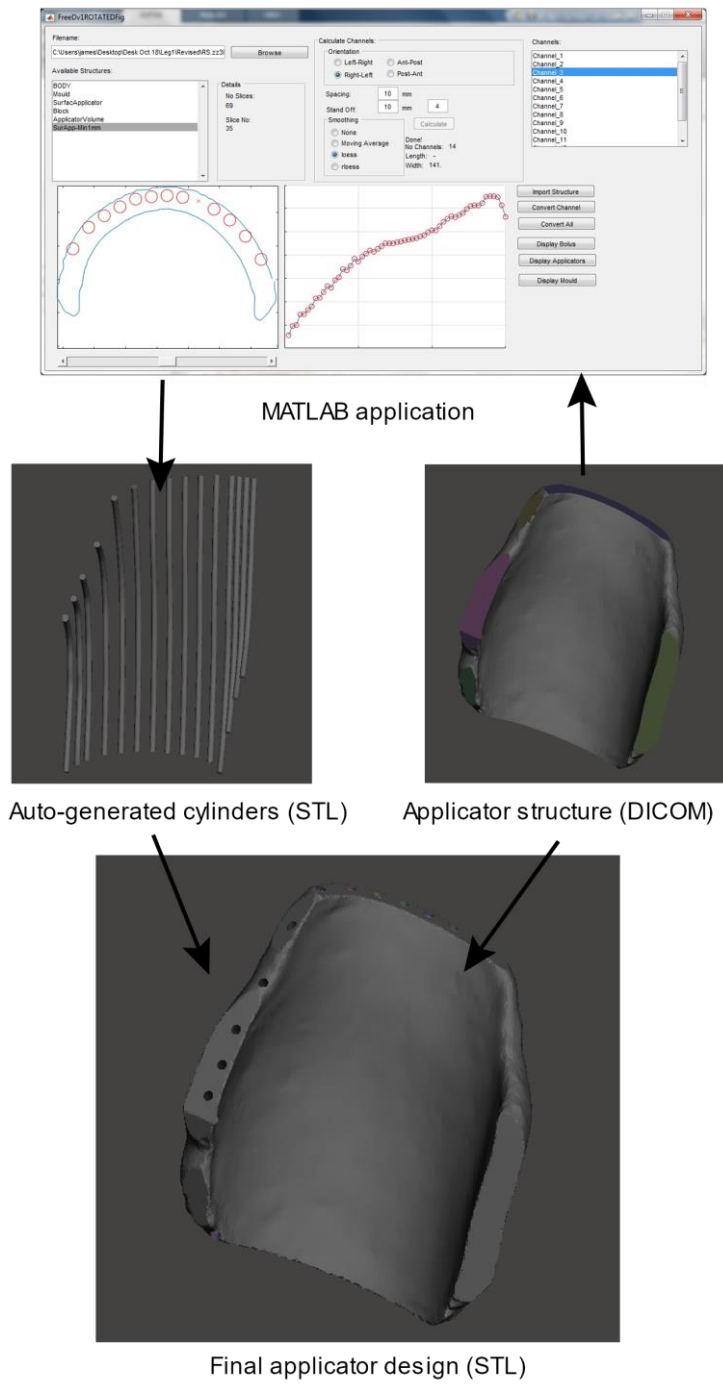


Figure 8 Simplified workflow to designing a brachytherapy surface applicator

3D-Printing

The final applicator design was exported from MeshMixer as a Stereolithography (STL) file to the open-source slicing application, Cura (Ultimaker, Utrecht, Netherlands). Cura is used to slice the 3D designs into thin layers and provide instructions specific to the 3D-printer and material in use in the form of G-code. For this study we used a Lulzbot® Taz 6 (Aleph Objects Inc. Colorado, U.S.A.) FDM type printer configured with the FlexyDually (Version 2) extruder (Aleph Objects Inc. Colorado, U.S.A.). The FlexyDually consists of dual extruders mounted on a single carriage, with the ability to print using both rigid and flexible materials at temperatures of up to 300°C. The filament material used was ABS, 3 mm in diameter (Keene Village Plastics, Ohio, U.S.A.). A wide range of settings can be configured within the slicing application some of which can have a significant effect on the suitability of the printed bolus for use as a tissue-mimicking material. Print settings were established based on manufacturers recommendations for using this particular ABS with the Taz 6 printer. Infill density was chosen based on a previous study of measurements of the water equivalence of ABS at various infill rates. A selection of the printer settings used are detailed in Table 5.

Parameter	Material Setting
Bed Temperature	110°C
Extruder Temperature	240°C
Layer Height	0.39 mm
Extrusion Width	0.6 mm
Print Speed	30 mm/s
Infill pattern	Cubic
Infill density	80%

Table 5 Sample of settings used when printing brachytherapy applicators using ABS in combination with the Taz 6 3D-printer

Ensuring that the printed material remains attached to the print bed can be difficult and is vital to successfully completing prints. The Lulzbot® Taz 6 has a heated print bed with a Polyetherimide (PEI) surface, designed to maximise surface adhesion. For all but the smallest prints, this was found to be inadequate and instead a 'raft' of sacrificial material was used as the base of the print in order to provide as large an initial surface area as possible. This extra material could easily be removed with the aid of pliers after the print had completed and helped prevent printed objects from warping during the printing process. In practice, we found this insufficient when using ABS and instead used a layer of Scotch blue masking tape (3M, Minnesota, U.S.A.) in combination with a thin layer of water-soluble adhesive (Pritt, Dusseldorf, Germany) and a large brim of sacrificial material designed to increase the surface area of the first printed layer. Printing took approximately thirty

hours to complete during which time it was remotely monitored via the Raspberry Pi and OctoPrint, Figure 9.

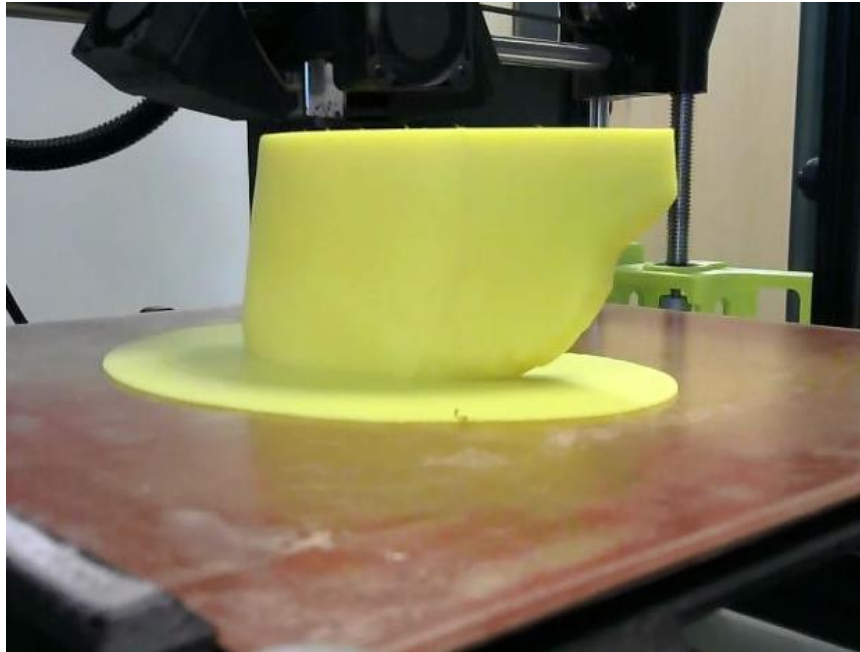


Figure 9 Remote monitoring of the 3D-printing process via a Raspberry Pi and the OctoPrint application

The total amount of material required was approximately 400 g with a material cost of £16. It is estimated that the total production cost was in the region of £170. This compared favourably to an estimated cost of £400 for a conventionally made applicator using thermoplastic shells and wax. Catheter guides were inserted into all but one of the channels, held in place with rubber O-rings and labelled so they could be easily and safely identified. A small pen marking was added to ensure the position of each catheter had not moved between treatments. The pointed ends of the catheters were shrouded

to prevent injury, see Figure 10. We were unable to easily pass a catheter through the one remaining channel due to a significantly curved trajectory that had not been noticed at the planning stage. It was decided not to use this channel for treatment due to the increased risk of the source becoming stuck within the applicator during transition and it was labelled accordingly.

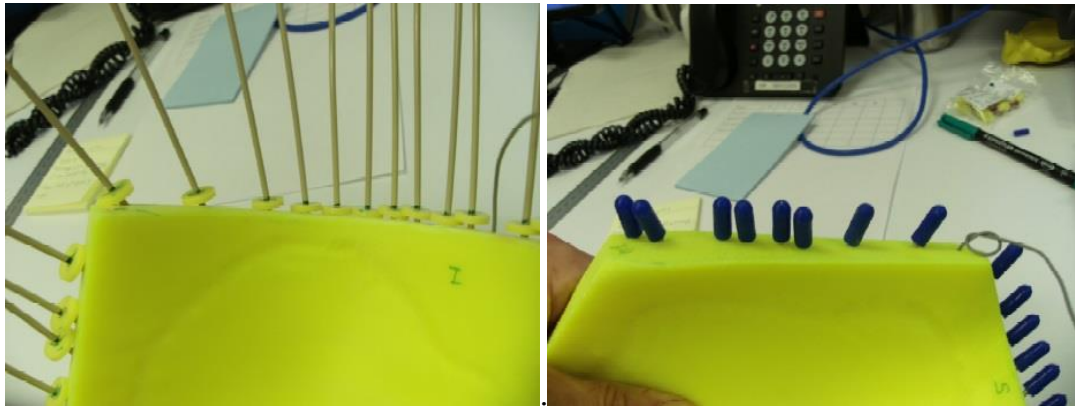


Figure 10 Sup and inf edges of the applicator with catheter guides in-situ demonstrating the rubber seals (Left) and shrouded ends (Right)

Applicator Quality Assurance

Following the production process and with the catheters in place, the applicator was CT scanned at 2 mm slice thickness and a comparison made to the initial applicator design to assess for accurate reproduction as well as structural integrity and homogeneity. This was done by manually fusing the CT scan of the applicator with the original patient data in such a way that it most closely matched the intended design and a qualitative assessment performed visually.

Treatment Planning

Patient planning was conducted using the BrachyVision™ TPS. The CT scan of the applicator was fused to the patient's planning scan using a series of ball-bearings for alignment. Radio-opaque guides inserted into each of the catheter filled channels were used to determine source trajectories, along which sources could be potentially positioned. The unavailable channel was tracked but labelled to prevent use. Each channel was identified according to the previously made physical labels. An initial plan of nominally defined dwells was optimised by adjusting isodose lines graphically within the TPS and subsequently scaled to the desired dose. A clinical plan was achieved that provided optimal dose to the PTV whilst limiting excess dose to the skin.

Treatment Plan Quality Assurance

An independent dose calculation of the planned treatment was carried out using an in-house excel spreadsheet based on the TG43 method [76]. The planned dose distribution was verified prior to treatment using MOSFET detectors placed between the applicator and skin surface during treatment; this process is standard practice for all custom surface moulds made within the department.

Treatment

The patient was treated using a GammaMed Plus HDR afterloader (Varian Medical Systems). The applicator was placed directly upon the patient's skin surface. An additional 3 cm of bolus material was added directly on top of the applicator in effort to maintain full scatter conditions. A photo of the applicator in-situ on the patient but without the additional scatter material is shown in Figure 11.

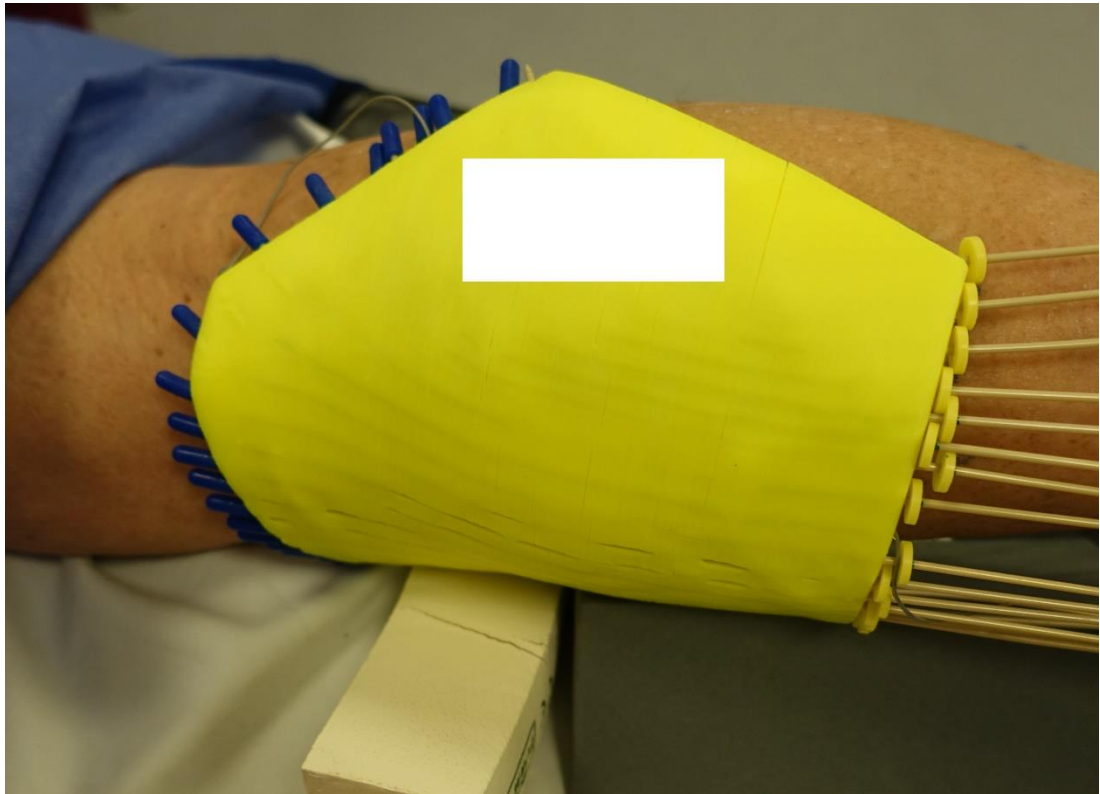


Figure 11 3D-printer applicator in-situ and connected to the GammaMed treatment unit

3.1.5. Results

Physical Integrity and Geometrical Accuracy

Once the issues maintaining bed adhesion were resolved, the applicator printed without incident. Some separation of individual layers was noted on closer inspection; this is commonly encountered when printing using ABS and is due to the cooling and subsequent contraction of upper layers. This can be observed at the lower edge of Figure 11. A small amount of post-processing was required, notably to remove excess material printed as a brim. When passing flexible catheters through each of the printed channels, most were found to be clear of any major obstruction. Where they were not, a flexible metal file was used to carefully remove the excess material. A CT scan at 2 mm slice thickness revealed good comparison to the initial applicator design, suggesting accurate placement and positioning could be obtained. A qualitative assessment revealed no significant areas of discrepancy and a satisfactory, homogeneously filled applicator. A maximum deviation between the printed and planned bolus was observed as approximately 2 mm. A single CT slice demonstrating discrepancy between the final printed bolus and planned applicator design is shown in Figure 12.

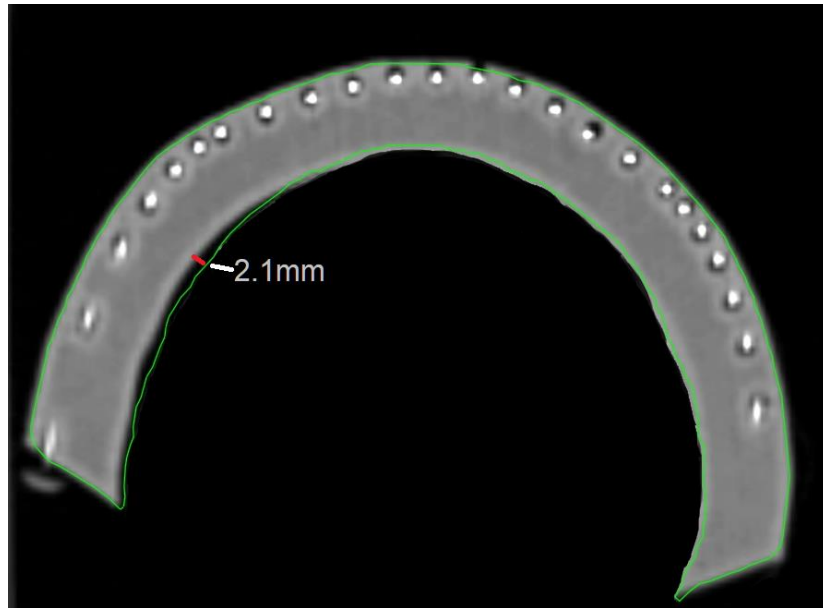


Figure 12 A CT scan of the final printed bolus with the green contour representing the planned applicator design

Treatment Planning

The channels were relatively easy to track due to the use of radio opaque catheters. A suitable planned dose distribution was achieved after a few hours and consisted of 473 individual dwells delivered via 22 channels. As well as the channel identified earlier, an additional channel was also found to be superfluous, this was due to its relative displacement from the PTV. A schematic representation of the final planned catheter and dwell positions in place upon the PTV is shown in Figure 13.

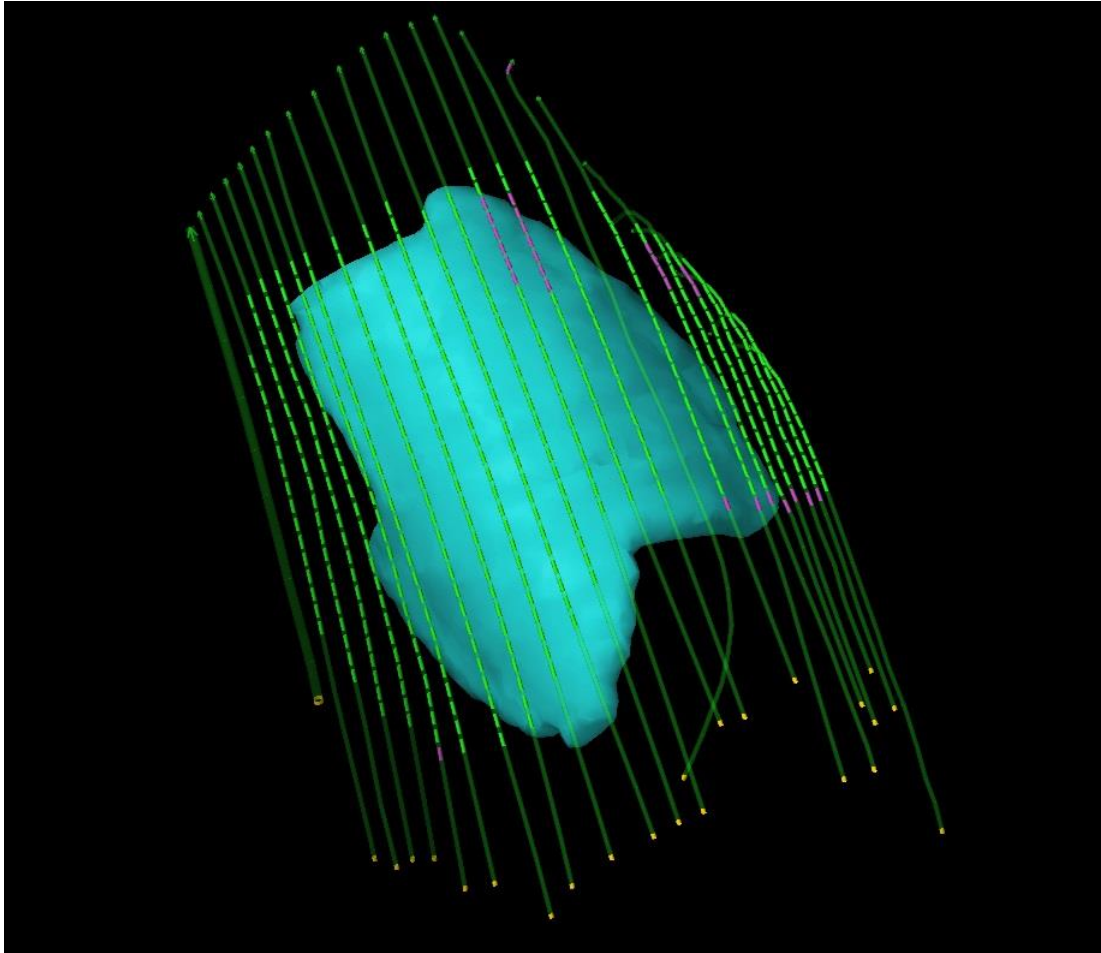


Figure 13 Schematic representation of catheter trajectories and dwell positions superimposed over the PTV

Quality Assurance

Using the TG43 method, an independent dose calculation indicated a -0.2% difference from that predicted by the BrachyVision™ TPS. Measurements made using MOSFET detectors revealed a potential 10% underdose when compared to the TG43 calculated dose. The TG43 algorithm assumes the radiation source to be uniformly surrounded by water equivalent medium. This assumption of full scatter conditions breaks down for skin

brachytherapy and so a patient specific correction factor was applied as is standard practice within the department.

Positioning

Immediately prior to treatment, a CT scan was acquired with the applicator in-situ, primarily so that the catheters could be accurately tracked. This gave opportunity to assess the positioning and fit of the applicator to the skin surface. A maximum discrepancy at any one point was observed to be approximately 4 mm and is shown in Figure 14. Such discrepancy was considered to be comparable to traditionally manufactured applicators but with reduced uncertainty when subject to repeat applications. In practice, gaps of this size may be compensated for during the treatment calculation stage and so it is important that they remain consistent throughout treatment to ensure the validity of the calculation is maintained.

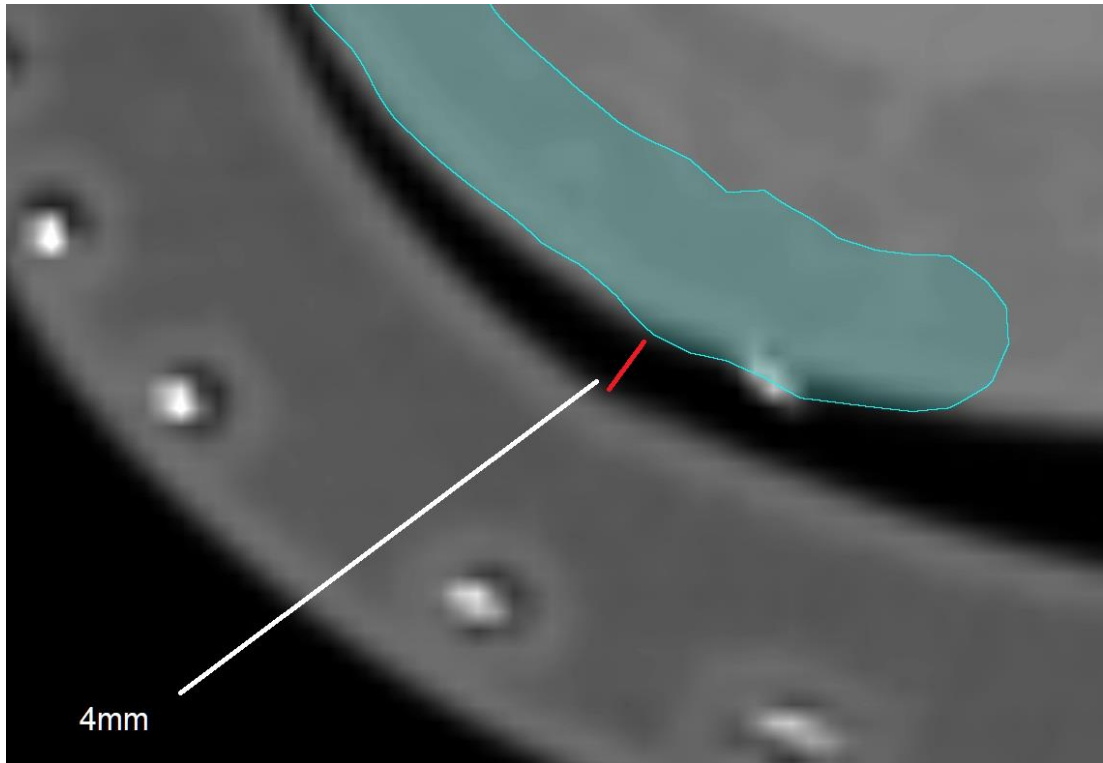


Figure 14 CT image of the catheter in-situ on the patient's skin surface showing a maximum displacement of approximately 4 mm

3.1.6. Discussion

This study was primarily aimed at assessing the feasibility of designing and manufacturing brachytherapy surface applicators using a combination of open-source software, in-house MATLAB code and a low-cost FDM style 3D-printer. The use of open-source hardware and software is common amongst a large extent of the research to date, likely due to the limited availability of commercially available alternatives. At this time, there is understood to be only one commercial system specifically designed for 3D-printing brachytherapy applicators [77]. Although we were not able to evaluate this

as part of this work, it is known to have been designed to work alongside open-source printers and slicing software.

Catheter Placement

In our study we designed an applicator with evenly spaced catheters positioned at set distance from the skin surface. Whilst a satisfactory plan source distribution was obtained, it is unlikely that this method allows for ideal source positioning. Indeed, it was only after an initial attempt had been made to plan the patient treatment that it became apparent such a large stand-off would be required. A better method may have been to create an ideal pre-plan within the TPS and converting dwell positions to catheter trajectories which could then be subsequently extracted from the solid applicator design as a series of curved cylinders. This is the method employed by Jones et al. who found discrepancy between pre-plan and pre-treat catheter positions did not exceed 2 mm and ensured only limited manipulation of the pre-plan was necessary [15]. A significant proportion of the time taken to plan was spent tracking the catheters within the applicator, there is therefore potential advantage to making no or only small modifications to the final catheter positions.

Percentage Infill

The applicator was printed at an infill of 80% as previous work (section 3.2) has shown ABS to be a satisfactory surrogate to water for a range of megavoltage energies used in radiotherapy at this rate. However, at the low photon energy range found within brachytherapy, the inverse square law dominates over the dose decrease due to absorption and scatter [51]. Rate of infill is therefore less important than the absolute positioning of catheters. A potential therefore exists for applicators to be printed with even lower infill percentage, limiting print time and material cost. It is anticipated that infill rates of below approximately 30-40% would be unable to sustain proper catheter guides.

Biological Considerations

Surface applicators are placed directly alongside the area to be treated, potentially in direct contact with the skin. Given disease, the skin may be broken or ulcerated presenting a risk of infection and complication. Ideally applicators should be sterile, easy to clean and biocompatible. Very few 3D-printed materials are available that fulfil such requirements and so a barrier between print and skin is commonly suggested, typically using plastic wrap [46]. Perez et al. [78] concluded that ABS derived materials could not withstand high temperature sterilisation techniques but could be successfully

sterilized by ethylene oxide gas, hydrogen peroxide gas plasma and gamma radiation. PC-ISO is a commercially available, biocompatible and sterilizable 3D-printer material and has been used in the manufacturer of gynaecological brachytherapy applicators. 3D-printers with the capability to print in FDA-approved materials such as PC-ISO are currently of the order of \$100,000 [79]. One option may be for centres to outsource printing to an external vendor. This would only be viable if it could be produced in an appropriate timeframe and with assurance of the safeguarding of potentially confidential and identifiable information.

Use of Flexible Filament Materials

The initial applicator design was printed in a widely available and well understood rigid plastic 3D-printer filament material. The final design proved a good reproduction of the original intended design which ensured it was well fitted to the patient's surface, assuming the patient's geometry remained the same. Both the 3D-printed and conventional wax-based applicators offer very little flexibility to anatomical change over a course of treatment. Flexible applicators that maintain fixed catheter positions, yet can accommodate subtle change to skin contour, may be preferential and would help maintain a fixed distance between the skin and the radiation source. Flexible 3D-printer materials have been used previously to manufacture

brachytherapy surface applicators [73] but the TangoPlus material used by Jones et al. is available for use only with expensive, industrial type printers. When equipped with a suitable printer tool head such as the FlexyDuall, the Taz 6 printer is capable of printing using flexible filaments. There are currently two commercially available printer filaments compatible with the Taz 6, NinjaFlex and Cheetah (Feener Inc., U.S.A.). As a preliminary investigation, the surface applicator studied here was 3D-printed using Cheetah flexible filament material. Flexible filaments are typically more difficult to work with, print at slower speeds and cost more than their rigid counterparts. The applicator took approximately fifty hours to print and required a considerable amount of post processing to clear the hollow catheter guides due to stringing caused by the release of filament whilst the hot-end travels between print locations. It is anticipated that the quality of the print could be improved with some tweaks to the print settings, adjusting the retraction, print speed or temperature in particular may help alleviate the stringing effects seen. Nevertheless, the applicator possessed a suitable amount of flexibility whilst maintaining enough strength to consistently support the catheter guides. Further verification of the physical and dosimetric properties of flexible printed filament materials at typical brachytherapy energy ranges is required but it is hypothesised that the small

uncertainties this would give rise too would be outweighed by the reduced positional uncertainties afforded using flexible applicators.

3.1.7. Conclusion

Using a low-cost 3D-printer in combination with various freely obtainable software, we were able to design and manufacture a custom surface brachytherapy applicator based on the patient's initial planning CT. Using anatomical information available from the CT removed the need for an additional mould room appointment which would otherwise have been required if we were to fabricate an applicator through more conventional means. This greatly improves the patient experience and the process was found to be more efficient and cost effective. The printed bolus provided good fit to the patient's surface at treatment and gave confidence that the planned source positions could be achieved to a good level of accuracy. There is scope for further optimisation of the design process and some preliminary work using flexible filament materials suggest a more comfortable and adaptable applicator could be achieved at the expense of increased cost and production time. 3D-printing offers an excellent means to produce applicators that are highly conformal to irregular surfaces such as the skin. The manufacturing process requires very little user input and so

may be of particular use to those departments without mould room facilities or with limited experience of producing brachytherapy surface applicators.

3.2 Flexible Filament Materials

Following on from the successful manufacture of a custom brachytherapy surface applicator and with increased interest and experience using flexible filament materials, a more detailed investigation into their dosimetric properties was undertaken. Ultimately the objective was to determine how best to account for flexible 3D-printed materials within the TPS and at what accuracy we could expect to deliver dose to a patient when using them.

3.2.1. Title and authors

The full title of the article contained within this sub-section is:

“Dosimetric properties of 3D-printed flexible filament materials in megavoltage photon beams”

The primary author of this article is James Burnley, with advice and contribution from Gerry Lowe, Rikki Ladd, Andrei Caraman, Jack Hills, Melvyn Folkard, Karen Venables and Geoff Budgell.

3.2.2. Abstract

3D-printing has been shown to be an effective means of manufacture of custom-made devices for use in external beam radiotherapy, particularly as bolus during photon treatments. Most clinical experience to date uses rigid thermo-plastics, notably acrylonitrile butadiene styrene (ABS) which can be difficult to use and offers little patient comfort or contingency for anatomical

change over the period of treatment. Using a low-cost, FDM style 3D-printer, the dosimetric properties of two commercially available flexible filament materials, Cheetah and NinjaFlex have been assessed. Their suitability for use in external beam photon radiotherapy is discussed and practical recommendations made for any implementation in a clinical setting. It is hoped this work will facilitate more widespread use of flexible 3D-printed materials for use as bolus, in phantom design, immobilisation and more.

3.2.3. Introduction

Tissue-mimicking bolus may be used during radiotherapy treatment to increase surface dose for superficial or shallow tumours where the skin-sparing effect offered using high-energy (MV) photons can be a disadvantage. Conventional methods of bolus production for complex patient geometries can be a challenging and labour-intensive process. Frequently, non-individualised, pre-fabricated bolus is used, which can lead to a poor patient fit and a subsequent reduction in the accuracy and effectiveness of treatment delivery. 3D-printing has been demonstrated as an effective means of manufacturing accurate, individualised bolus, in a range of materials, notably rigid plastics. The purpose of this study is to evaluate two commercially available semi-flexible materials, NinjaFlex® and Cheetah™ (Feener Inc., U.S.A.), used in conjunction with a low-cost fused

deposition modelling (FDM) style 3D-printer for radiotherapy purposes. The radiation properties of these materials in 6 MV and 10 MV photon beams are evaluated, and comparisons are made to ABS (a commonly used alternative rigid plastic) and water. The geometric accuracy and reproducibility, as well as any relevant practical considerations such as ease of use and cost are also considered and discussed.

3D-Printing

3D-printing has been implemented for a wide range of uses within radiotherapy, notably in the production of patient bolus, immobilisation devices, QA phantoms and brachytherapy applicators [80] [46] [39] [35] [12]. Most experience reported to date uses a combination of relatively inexpensive FDM style printers and rigid plastics, notably ABS and polylactic acid (PLA). This is likely due to its widespread availability and its relative density being close to that of water. For high energy (MV) photon radiotherapy where Compton scattering predominates, physical and electron density have the greatest effect on absorbed dose [46]. Materials used for radiotherapy purposes should ideally be tissue-equivalent with properties similar to that of water. The physical properties of a range of commercially available materials used with FDM style printing are summarised in Table 6.

Unfortunately, no measure of electron density could be found in the literature for either of NinjaFlex or Cheetah materials.

	ABS	PLA	NinjaFlex	Cheetah
Physical Density (g/m ³)	1.04[46]	1.2[46]	1.2[81]	1.2[82]
Electron density (relative to water)	1.01[46]	1.14[46]	-	-

Table 6 Physical properties of ABS and PLA versus the flexible materials NinjaFlex and Cheetah

Despite successes in a clinical setting [46], ABS does not offer the physical flexibility of some of the materials it has replaced, and the lack of malleability is often cited as a source of patient discomfort when using bolus [14] [83].

Despite being able to print ABS to close tolerances, contoured individually to a patient surface, having the ability to manually adjust the shape and curve of a bolus may improve patient fit and comfort. Radiotherapy courses are typically delivered over a period of weeks and anatomical change can necessitate adjustment to the bolus. Flexible bolus could potentially negate the need for re-printing ill-fitting bolus, saving time and cost.

3.2.4. Materials and Methods

3D Design and Printing

The various shapes and sizes of material used were designed using the Fusion 360 CAD package (Autodesk Inc. California, U.S.A.) and exported as

Stereolithography (STL) files to the open-source slicing application, Cura (Ultimaker, Utrecht, Netherlands). Cura is used to slice the 3D designs into thin layers and provide instructions specific to the 3D-printer and printing material in the form of G-code. For this study we used a Lulzbot® Taz 6 (Aleph Objects Inc. Colorado, U.S.A.) FDM type printer configured with the FlexyDually (Version 2) extruder (Aleph Objects Inc. Colorado, U.S.A.). The FlexyDually consists of dual extruders mounted on a single carriage, with the ability to print using both rigid and flexible materials at temperatures up to 300°C. The filament used was 3 mm in diameter. ABS was manufactured by Village Plastics (Keene Village Plastics, Ohio, U.S.A.), NinjaFlex and Cheetah by NinjaTek (Feener Inc., U.S.A.). A wide range of settings can be configured within the slicing application, some of which can have a significant effect on the suitability of the printed bolus for use as a tissue-mimicking material. Using linear infill patterns at low density in particular can result in columns of air that traverse the length of print. In order to minimise potential orientation effects, an infill pattern that rotates with each layer was used. A selection of printer settings used for each material type is detailed in Table 7.

	ABS	NinjaFlex	Cheetah
Bed Temperature	110°C	40°C	40°C
Extruder Temperature	240°C	225°C	230°C
Layer Height	0.39 mm	0.39 mm	0.35 mm
Extrusion Width	0.6 mm	0.6 mm	0.6 mm
Print Speed	30 mm/s	20 mm/s	60 mm/s
Infill pattern	Cubic	Cubic	Cubic
Infill density	80%	80%	80%

Table 7 Sample of settings used for a range of materials in combination with the Taz 6 3D-printer

Ensuring that the printed material remains attached to the print bed can be difficult and is vital to successfully completed prints. The Lulzbot® Taz 6 has a heated print bed with a Polyetherimide (PEI) surface, designed to maximise surface adhesion. In practice, we found this was inadequate when using ABS and instead used a layer of Scotch blue masking tape (3M, Minnesota, U.S.A.) attached to the print bed and coated this with a thin layer of water-soluble adhesive (Pritt, Dusseldorf, Germany).

CT Number and Physical Density

A selection of inserts were designed specifically for the CIRS 062 electron density phantom (CIRS, Norfolk, VA, U.S.A.). A minimum of two inserts were printed for each rate of infill being investigated. Each insert was subsequently imaged within the phantom using a Siemens SOMATOM Definition AS CT scanner (Siemens Healthcare, Erlangen, Germany) in order

to obtain average Hounsfield units for each insert in effort to determine relationship to physical density. TPS estimated density was compared to physical density obtained from measurements of mass and volume obtained using a scale and digital callipers. The printed bolus was compared and evaluated qualitatively against its intended design for geometrical accuracy and physical integrity. In practice, printing at 100% infill rates was found to have a significant impact on print time and led to an excessive reduction of the flexibility afforded by the materials. Cheetah in particular, offered very little flexibility when printed at infill rates above approximately 80%. Subsequently an infill of 80% was used for the remainder of the study as this provided good compromise between flexibility and print time. Although this was not quantified, flexibility of the materials at such infill rates was considered comparable to existing commercial bolus materials. Attenuation through 5 mm of each material was measured using a single 5 mm thick slab and a Markus plane-parallel ion chamber (PTW, Freiburg, Germany) set 5 cm deep inside a WT1 water equivalent phantom (St. Bartholomew's Hospital, London, UK).

Tissue Maximum Ratio and Percent Depth-Dose Measurements

Tissue maximum ratio (TMR) and percentage depth dose (PDD) quantify the change in radiation intensity as it passes through a medium. PDDs relate the

dose at a point in a radiation beam's central axis to the dose at the depth of maximum dose (d_{\max}) for a specific beam in a fixed phantom. PDD is dependent on the source to surface distance (SSD) and is useful when calculating treatment dose at a specific, fixed SSD. TMR is the ratio of dose at a given point and depth in a material to dose at the same point at the depth of maximum dose. TMR is independent of SSD and so is useful when calculating treatment dose delivered isocentrically, i.e. at a fixed distance from the source of radiation. TMR and PDD measurements were performed using a Markus chamber set inside a WT1 water equivalent phantom, see Figure 15. For TMR measurements, the chamber was set at isocenter and printed slabs 12 cm × 12 cm in size and in thickness of 2, 4, 5 and 10 mm were combined up to a total of 40 mm. Two hundred MUs of both 6 MV and 10 MV photons were delivered using a 4 cm × 4 cm field on a Varian TrueBeam® linear accelerator (Varian Inc. Palo Alto, U.S.A.). PDD measurements were made using the same printed blocks placed on top of the ion chamber whilst maintaining a SSD of 100 cm. Both TMR and PDD measurements were compared to measurements made in water and to data calculated from the Eclipse treatment planning system (TPS) (Varian Inc. Palo Alto, U.S.A.) using the calculated electron density values determined from the attenuation measurements as detailed in section 3.2.5.

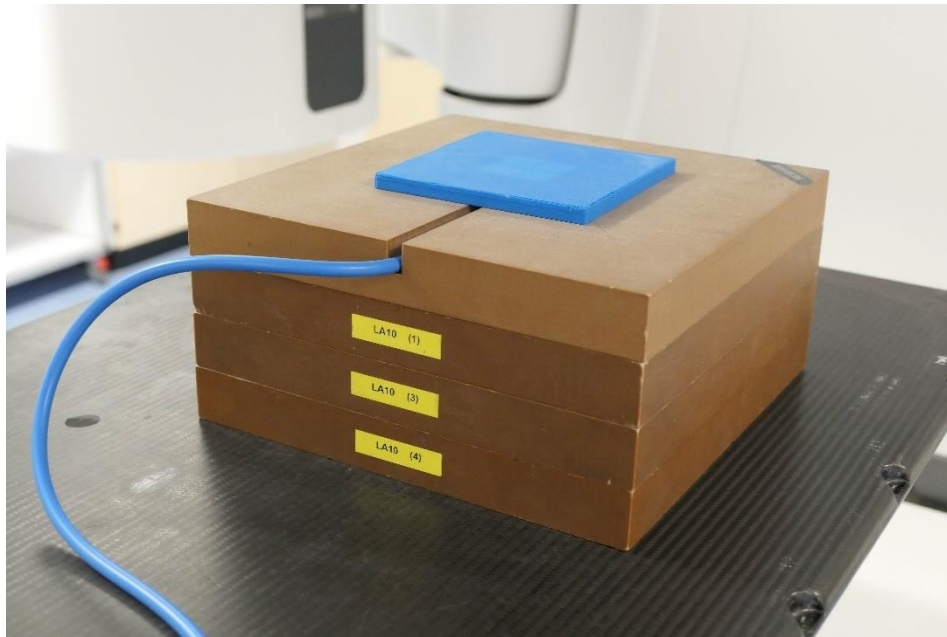


Figure 15 Experimental setup for measurement of PDD and TMR

Plan Analysis

A clinical VMAT plan to be delivered close to the skin surface in the head and neck region, identified as benefitting from use of bolus was transposed on to a geometrical representation of the Delta⁴ verification phantom (ScandiDos, Uppsala, Sweden). The plan was delivered via two arcs, delivering a total dose of 55 Gy over a course of 20 fractions to a volume of approximately 114 cm³. An additional 0.5 cm of approximately 12 cm × 12 cm bolus was included to cover the anterior aspect of the intended treatment volume. Approximately 55% of the total treatment was identified as being delivered in part through the bolus material. This bolus structure was subsequently used to produce a 3D model which could then be printed in

any of the desired materials. An exported DICOM structure of the bolus was converted to an STL file type using the open-source 3DSlicer software (<http://www.slicer.org>). The model was then smoothed and further prepared for printing using the freely available MeshMixer (Autodesk Inc. California, U.S.A.) modelling software. Plans were calculated for each of the three bolus materials, using the previously determined CT numbers as overrides, and were delivered to the phantom in turn using the Varian linear accelerator with the printed bolus in-situ, see Figure 16. A CBCT image was taken for each of the three bolus set-ups to help further assess accuracy of the production process. Using the Delta⁴ software, calculated and delivered plans were compared via the gamma analysis method [84] using a global gamma index, with a dose threshold of 20% and a pass/fail criteria of 2%/2 mm. All Delta⁴ measurements were suitably corrected to provide measure of absolute dose.

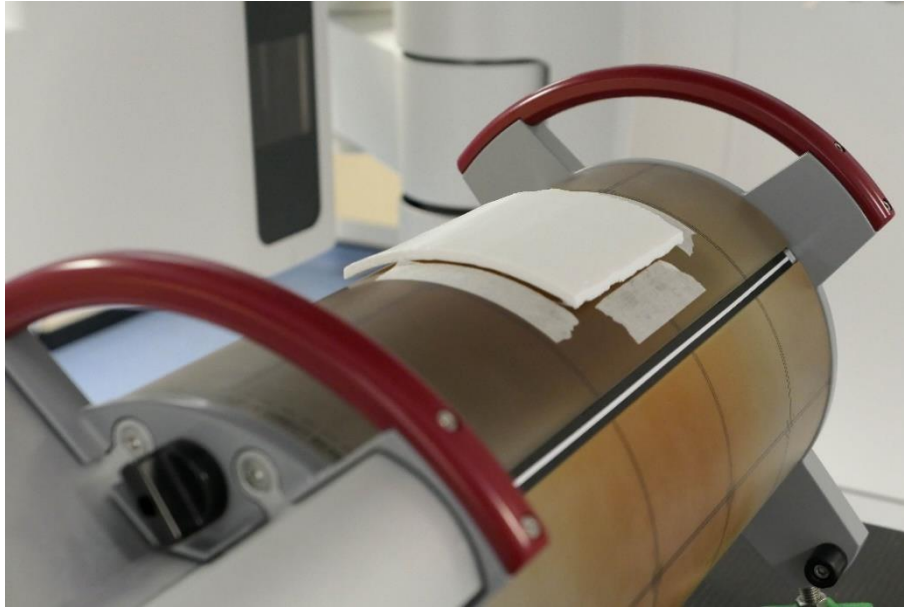


Figure 16 3D-printed bolus in-situ on the Delta⁴ phantom

3.2.5. Results

Geometrical Accuracy, CT number and physical density

Volume measurements for each of the printed inserts ranged from 59.8 cm³ to 62.6 cm³ with an average of 60.6 cm³. This compared well to the expected volume (60 cm³) suggesting good reproducibility could be obtained using all three materials. Visual checks of the planned versus printed bolus using CT images of each of the three inserts, revealed discrepancies of up to approximately 2 mm at any one point. A cross section CT image of two of the printed inserts is shown in Figure 17.

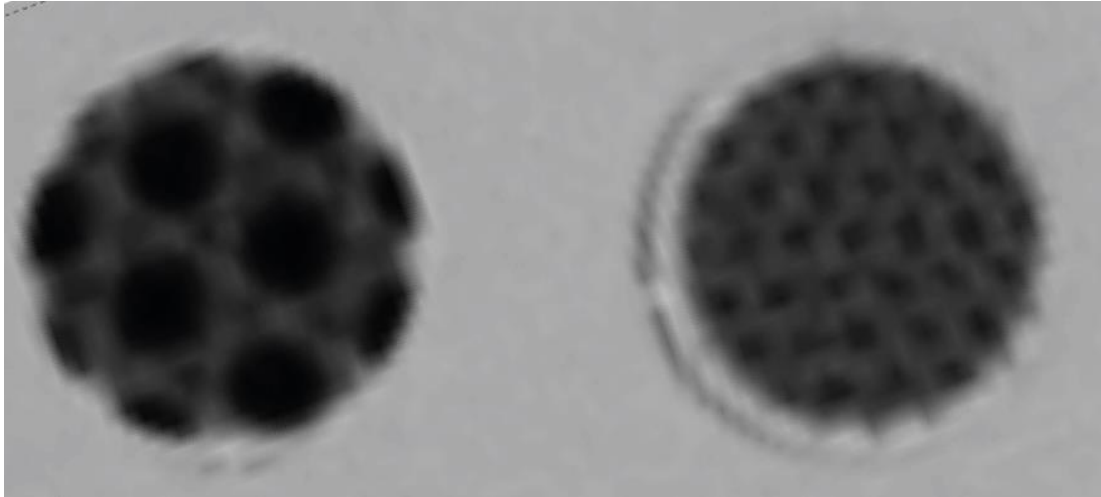


Figure 17 High resolution image of two of the printed NinjaFlex inserts printed at 20% infill (Left) and 50% infill (Right)

Density measurements suggested an approximate linear relationship with infill percentage for both ABS and Cheetah materials, see Figure 18. For NinjaFlex, printing at infill above approximately 90% produced no noticeable increase in density. However, it became apparent during printing, that when printing at high infill rates with NinjaFlex, an excess of material could prevent a free flow of filament. An accurate account of NinjaFlex at infill rates of above approximately 90% was therefore unlikely obtained. All three materials shared approximately the same density value at the 80% infill rate, determined as 0.81 g/cm^3 .

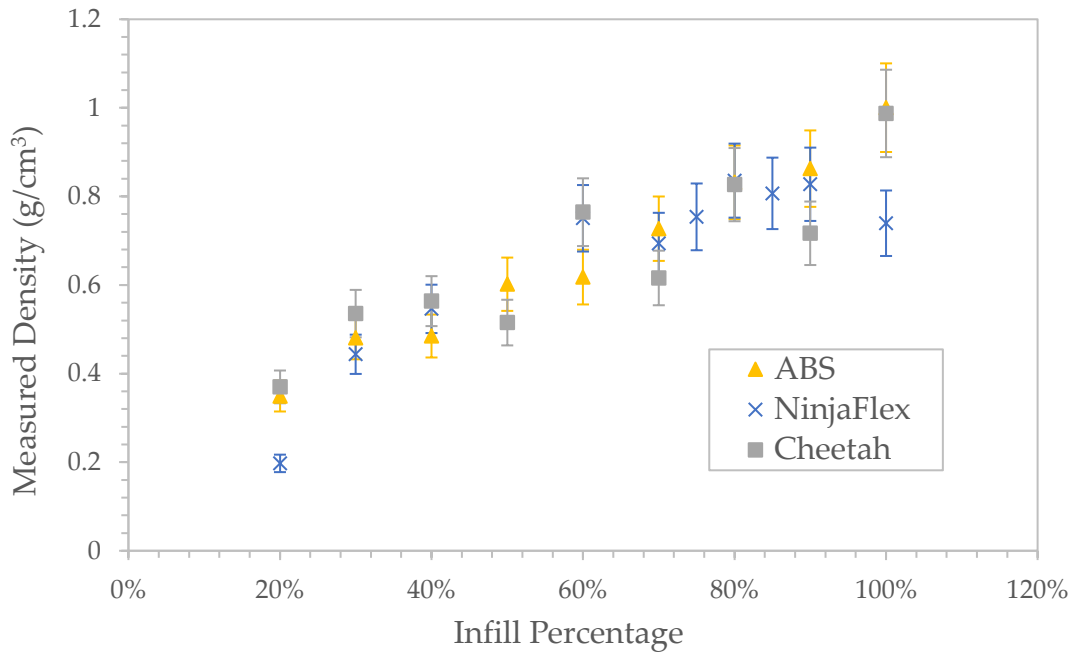


Figure 18 Measured density as a function of infill percentage in each of the three 3D-printed inserts

A CT scan of the inserts revealed variable agreement between CT number and infill rate for each of the three materials. Good overall agreement was observed at the 80% infill rate, see Figure 19.

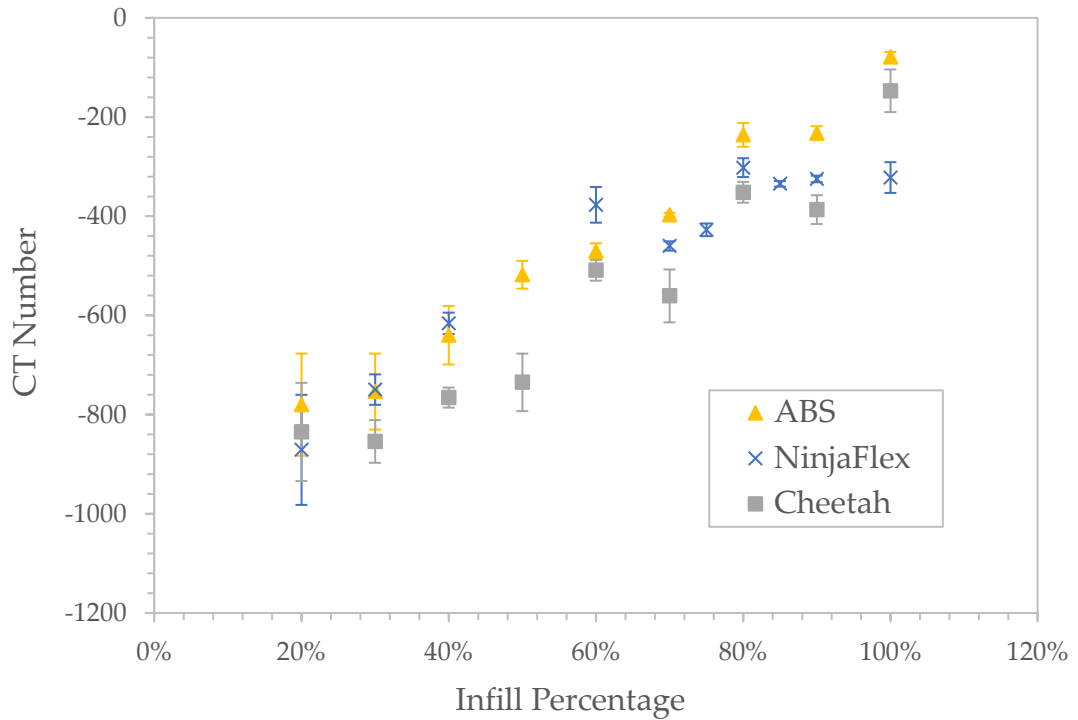


Figure 19 Infill percentage versus CT Number for each of the three 3D-printed inserts

Discrepancy of up to 24% was seen between measured density and that predicted by the TPS through interpretation of the CT data. Analysis of three repeat prints at the 80% infill rate suggest flexible filaments may produce prints with similar uncertainty compared to ABS. A summary of the average CT numbers, measured densities and TPS predicted densities, for each of the three materials at the 80% infill rate and a water equivalent insert is given in Table 8.

Insert	CT Number	TPS Predicted Density	Measured Density (g/cm³)	Difference (TPS Vs Measured)
ABS	-259±32	0.76±0.04	0.80±0.04	-5%
NinjaFlex	-309±9	0.71±0.01	0.78±0.08	-9%
Cheetah	-364±12	0.64±0.01	0.84±0.02	-24%
Solid Water	-17±14	1.000±0.001	0.95±0.01	5%

Table 8 CT number and measured versus TPS calculated densities of ABS, NinjaFlex and Cheetah printed inserts at 80% infill rate compared with measurements of a solid water insert

Printed thicknesses of individual slabs used for the attenuation measurements were assessed and ranged from 4.8 mm – 5.4 mm with an average thickness of 4.9 mm.

Attenuation through 5 mm of each of the 3D-printed materials and the commercially available WT1, was measured and compared, and is summarised in Table 9. The maximum range of differences between the 3D and WT1 materials was determined as 0.8% and 0.6% for 6 MV and 10 MV respectively.

Attenuation (5 mm)		
	6 MV	10 MV
ABS	-1.7%	-1.3%
NinjaFlex	-1.3%	-0.9%
Cheetah	-1.7%	-1.2%
WT1	-2.1%	-1.5%

Table 9 Attenuation through 5 mm thickness material slabs for 6 MV and 10 MV photon beams at 80% infill

For each of the 3D-printed materials, attenuation through a single 5 mm slab was compared to attenuation through 5 mm of bolus made up of five individual 1 mm slabs. A maximum increase in attenuation of 1.1% was observed, likely due to the wall thickness parameter effectively rendering such prints at closer to 100% infill.

The experimental attenuation scenario was replicated in the TPS and the density of an equivalently sized bolus was varied in order to establish which density value best represented the measured attenuation. Results for 6 MV and 10 MV were averaged and are detailed in Figure 20. A summary of the correspondingly calculated CT override is given in Table 10.

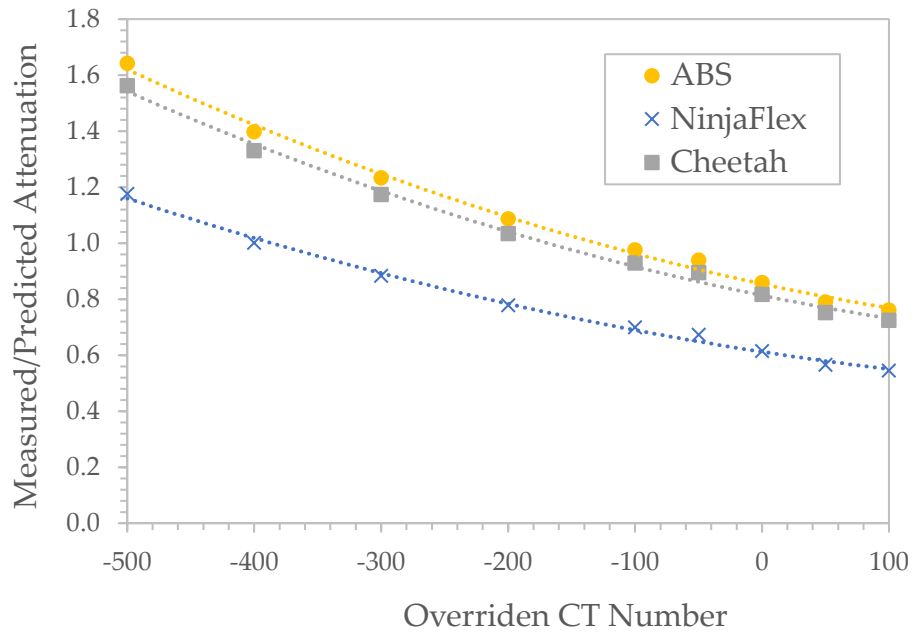


Figure 20 The effect of CT override on measured/planned attenuation for 6 MV and 10 MV averaged in order to obtain a match to measured data

	TPS Predicted Density	Measured density	Calculated Density	Difference from TPS	Measured CT	Calculated CT Override
ABS	0.76	0.80	0.917	21%	-259	-124
NinjaFlex	0.71	0.78	0.601	-17%	-309	-394
Cheetah	0.64	0.84	0.869	36%	-364	-165

Table 10 Summary of density variations and calculated CT override for each of the three 3D-printed filaments

TMR and PDD

Thickness of individual slabs used for the TMR and PDD measurements were verified using digital callipers and demonstrated an obtainable accuracy of approximately ± 1 mm across a range of sizes.

Calculated TMR curves for both flexible materials were compared to both ABS measurements as well as measurements made within water and are shown in Figure 21. The difference between the TMR curves for the three printed materials is less than 7%, indicating that similar results would be achieved when using them as bolus, regardless of the material used. At 6 MV, compared with water, ABS exhibited a maximum deviation of 6% at 5 mm, NinjaFlex a maximum deviation of 13% at 5 mm and Cheetah a maximum deviation of 10% at 5 mm. This was unsurprising given the preceding density results and the fact that the materials were all printed at the 80% infill rate. Results were similar at 10 MV. TMR curves for both NinjaFlex and Cheetah materials rose less sharply than those for water and ABS and fell more gradually beyond the depth of maximum dose.

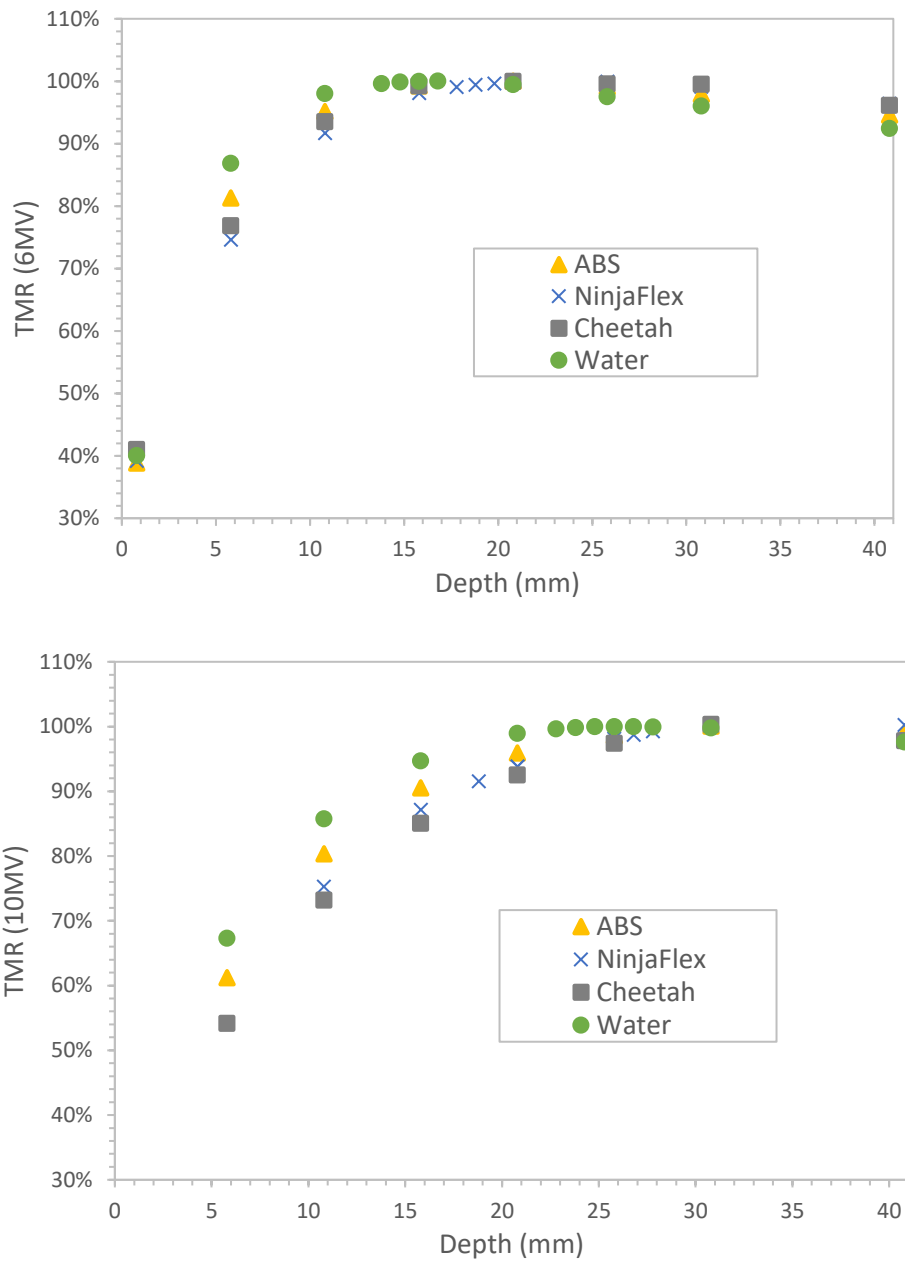


Figure 21 TMR Curves comparing ABS, NinjaFlex and Cheetah 3D-printed materials with water at 6 MV (Top), 10 MV (Bottom)

PDD curves for all three materials for both 6 MV and 10 MV with dashed lines representing TPS data calculated using the CT override established in the previous section are shown in Figure 22.

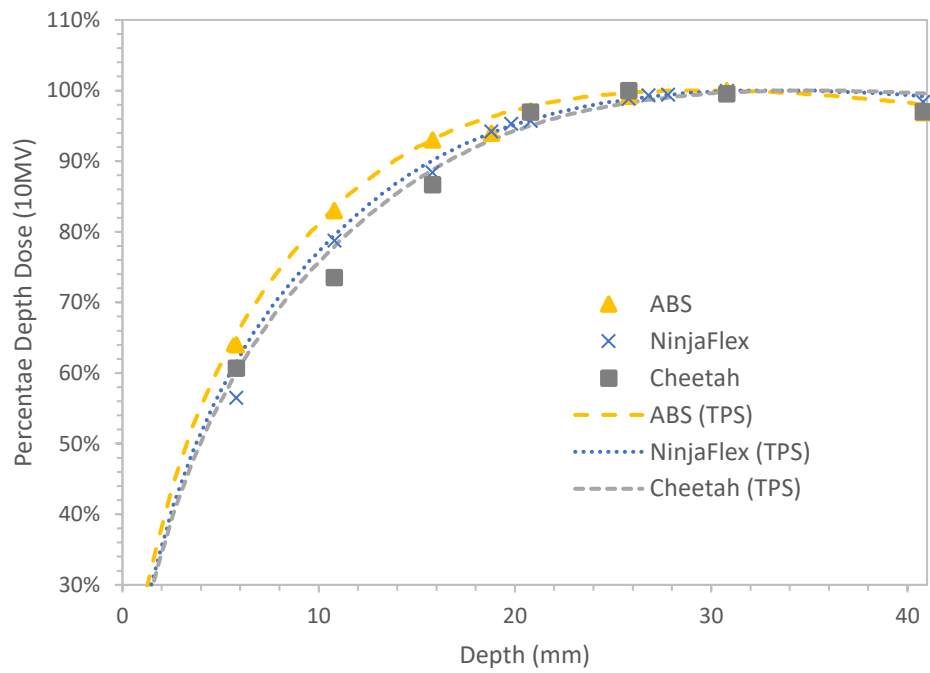
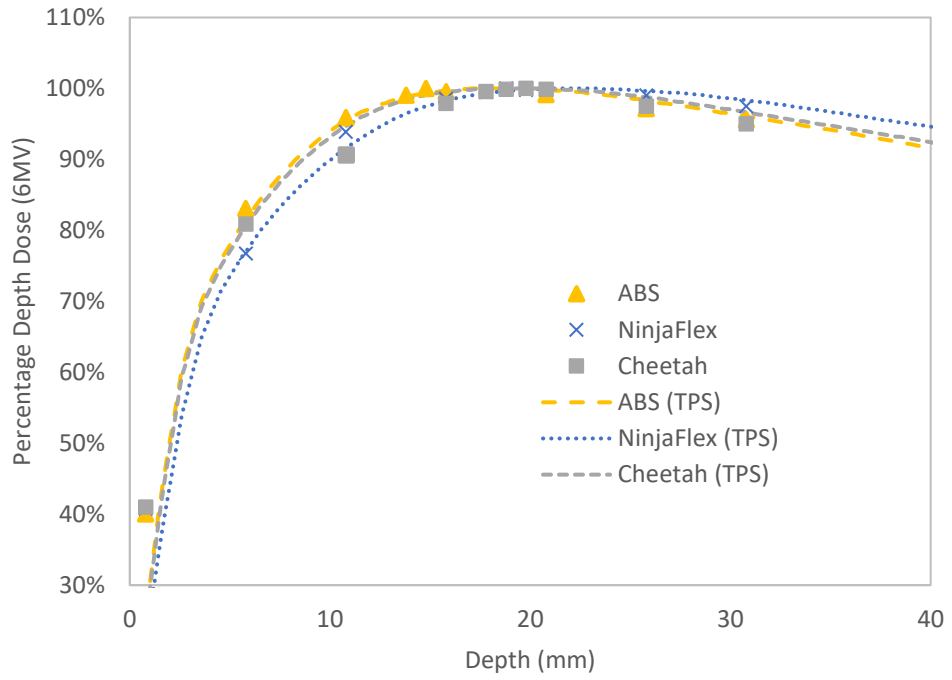


Figure 22 PDD Curves comparing ABS, NinjaFlex and Cheetah 3D printed materials at 6 MV (Top) and 10 MV (Bottom)

ABS measurements were in reasonable agreement to the calculations made in water whilst both Cheetah and NinjaFlex were better represented using their approximately corresponding override, particularly in the build-up region.

Plan analysis

The calculated dose distributions are shown in Figure 23 for both the patient and Delta⁴ plans.

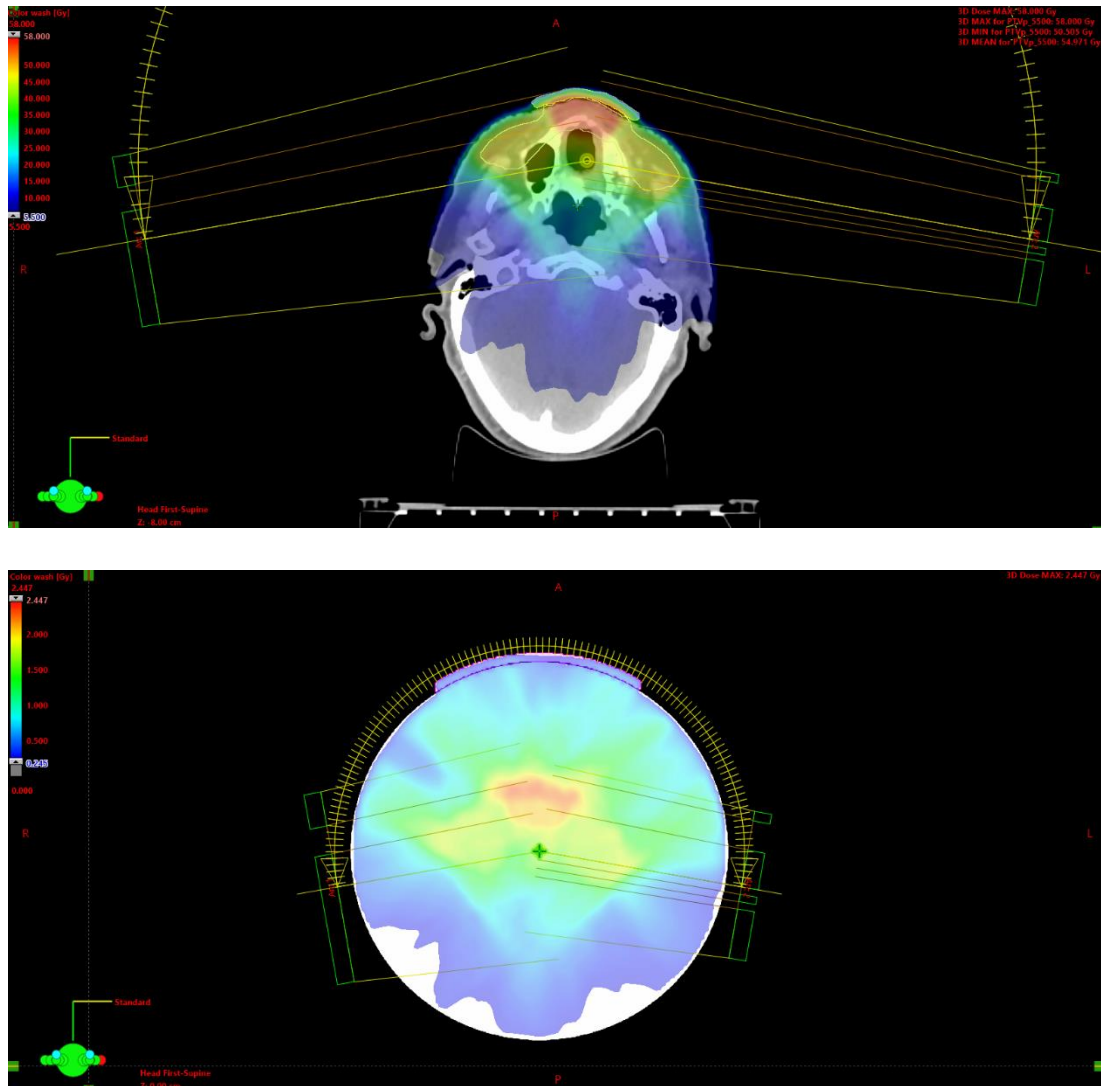


Figure 23 Calculated dose distributions for the clinical treatment plan (top) and Delta⁴ verification plan (bottom)

The results of the gamma analysis of each of the three calculated bolus plans as well as the original plan (without bolus) is summarised in Table 11.

Inclusion of bolus material increased error in the plan as indicated by lower gamma pass rates, however all three bolus plans met the tolerance criteria set out in our department for clinical suitability. The lowest gamma result was observed when using ABS, likely due to the slightly poorer geometric

reproduction and fitment as indicated by CBCT of the bolus in situ at the time of delivery, see Figure 24. A maximum variation of approximately 2 mm was observed between the expected and physical bolus position for each of the three materials. Although likely to have some effect on the sensitivity of the verification measurements, this variation is thought to be comparable to that found using existing commercially available bolus materials. The printed ABS was also subject to some layer separation which also would have affected its placement and fit to the Delta⁴ phantom. The Ninjaflex material fitted best to the phantom, most likely due to its increased flexibility.

	Dose Deviation	DTA	Gamma 2%/2 mm
No-bolus	90.5%	99.6%	97.8%
ABS	88.1%	99.3%	96.7%
NinjaFlex	89.4%	98.9%	97%
Cheetah	88.3%	99.3%	97.6%

Table 11 Gamma analysis for each of the predicted plans

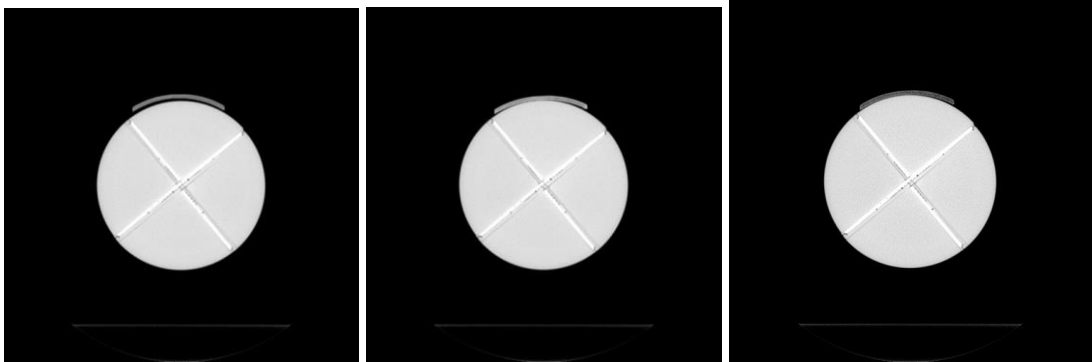


Figure 24 Placement/fit of the three 3D-printed boluses in-situ on the Delta⁴ phantom, ABS(Left), Cheetah(Centre), NinjaFlex(Right)

As can be seen from Figure 24, the Delta⁴ phantom consists of a 'pair' of detector boards orientated orthogonally to one another. It is therefore not possible to place the bolus directly upon the detectors and dose between the detectors and at the surface of the phantom can only be predicted. More accurate assessment of difference may be obtained using verification phantoms consisting of detectors arranged on the surface of a cylindrical phantom, such as the ArcCHECK[®] array (Sun Nuclear Corporation, Melbourne, FL). Measurement sensitivity using alternative equipment may be compared through assessment of a calculated bolus plan measured without bolus in place.

3.2.6. Discussion

One of the most prominent applications of 3D-printing within radiotherapy to date has been in the production of patient specific bolus used to increase

surface dose for treatments to the skin, eyes or other superficially located disease. The challenge of producing tissue-mimicking bolus starts in finding a dosimetrically equivalent material that can be accurately matched to complex surface irregularities. Thermoplastic materials such as ABS or PLA, used in combination with a 3D-printer can achieve this but the physical properties of these materials result in fixed, rigid designs which offer little contingency for anatomical change over the course of a typical radiotherapy treatment. Whilst physically less equivalent to water, flexible printer filaments such as Cheetah and NinjaFlex can be used to produce highly accurate and stable bolus, in which, radiation dose can be accurately modelled using a TPS. Whilst challenging, potentially slower and more costly compared with rigid materials, 3D-printing of flexible materials is entirely viable and finished prints were seen to be less prone to compromise in the form of structural irregularities and failure as can typically be encountered when using ABS. The work presented here may be used as the basis for the commissioning of flexible filament materials for clinical purposes. This process should characterise the geometrical accuracy and reproducibility of printed designs, the dosimetric properties and water equivalence of the material for the desired radiation and suitability for its

intended use with patients.

Geometrical Reproducibility

Accurate geometrical production of bolus is crucial in order to maintain good fit to the patient surface. This can be difficult to achieve with commercially produced flat-form bolus which can reduce both the dose coverage and dose homogeneity in the target volume [48] [52]. 3D-printed bolus was seen to provide good surface fit to a variety of complex geometries [52] [53].

However discrepancies of up to 2 mm suggest some form of QA may be required [53] and an acceptable tolerance, likely to be of this magnitude, is agreed. Structural inconsistencies can also reduce the effectiveness of printed bolus. Fortunately, due to the nature of manufacture, FDM style printing does not usually result in internal defects without an obvious overall failure of the print. Notwithstanding, at high infill rates using NinjaFlex in particular, reduced material flow rate and subsequent production of spongy, hollow bolus was experienced. Such defects were not immediately obvious externally and could only be fully assessed through internal inspection. A CT scan to verify geometry of the printed bolus and confirmation of an appropriate density is recommended. Quantitative assessment may be carried out by fusing imaging of the bolus with the original planning CT and assessing areas of maximum discrepancy between the scanned and intended

bolus contours. A maximum deviation of 2 mm is considered to be appropriate given the accuracy of most currently available FDM printers and the clinical significance of any subsequent changes to dosimetric effect. The effect of orientation was assumed to be negligible given the choice of infill pattern and density used in this study but further investigation may be sought when using alternative patterns and/or density.

Water Equivalence

Conventionally when considering any potential bolus material, strong emphasis has been made to ensure that it is as equivalent to tissue or water as possible. While this may still be important for plans calculated based on interactions within water, IMRT planning algorithms are more easily adapted to accommodate for such inhomogeneities and so the issue becomes less of a concern provided the calculation accuracy can be maintained. The importance lies therefore in accurate assignment of electron density to the material within the TPS whilst ensuring that the intended purpose of the bolus, i.e. to provide sufficient surface dose, can also be met.

Investigation using scanning electron microscopy has shown materials such as PLA to be good match to human tissue in terms of elemental compositions, CT numbers and mass attenuation coefficients [85]. Elemental composition of propriety 3D printed materials such as NinjaFlex can be hard

to obtain. Where the inclusion of elements with an atomic number beyond which was used to generate a CT calibration curve cannot be ruled out, assigning density should not be based on information obtained via CT alone. Ideally this should be done using measurements of attenuation within the intended radiation beam quality and calculation of dose for the expected clinical thicknesses of bolus to be used.

Clinical Suitability of Materials

For those designs, intended to be used in direct contact with a patient surface, consideration must also be made to the materials biocompatibility and its use in accordance with any relevant medical device laws and legislation. In the U.K., 3D-printed objects intended for patient use would be classified as medical devices and, although specific exemptions exist and may be applicable, they are not exempt from general safety and performance requirements and their use should be justified [86]. For non-biocompatibility approved materials such as NinjaFlex and Cheetah, introducing a physical barrier between the patient and the 3D-printed material has been suggested in an effort to maintain sanitary conditions [46]. Without a suitable alternative, this would be worth considering as a minimum.

Quality Assurance

Following any assessment or characterisation of flexible filament materials a detailed record of the printing parameters used should be maintained. These parameters may usually be established as specific printing profiles within most slicing software. As part of the commissioning process a program of quality assurance should be devised to help ensure these parameters and their intended outputs are preserved. Such measures may include the assessment of test objects of known physical size and density and those intended to evaluate specific printer capabilities, i.e. bed adhesion, print speed, resolution.

3.2.7. Conclusion

Characterisation of the dosimetric properties of both Cheetah and NinjaFlex flexible 3D-printed materials has been investigated and a method to compensate for any non-water equivalence has been proposed based on their intended use as bolus materials at low thicknesses. It is hoped this work will help facilitate more widespread use in a radiotherapy setting. Whilst specific printer recommendations have been made here, it should be noted that these may require adjustment dependent on the specific printer model and filament batch used and as such should be investigated in an individual setting prior to any clinical implementation. It is also likely that the optimal

parameter settings for 3D-printing with such materials has not yet truly been realised. Modification of infill rate in particular can have a significant effect on the dosimetric properties of a printed object but can also adversely effect the flexibility afforded by such materials. A compromise must be sought between high infill for strength and water-equivalent densities and low infill for flexibility and better fitting, more adaptable designs.

Finally, further characterisation of these material may be required particularly for specialist use with brachytherapy, electron and kilovoltage radiotherapy.

3.3 Radiotherapy Bolus Using Flexible 3D-printed Materials

With better understanding of the dosimetric properties of flexible filament materials and a means to accommodate for any non-water equivalence of bolus planned using them, clinical implementation followed and is now considered fully established within the radiotherapy department at the Mount Vernon Cancer Centre. Bolus is typically used for head and neck patients, planned and fitted to the outside of a patient's thermoplastic treatment shell. After some time, an opportunity presented requiring bolus within the patient themselves and was documented as a clinical case study. Various other patients have since been treated using the techniques discussed here.

3.3.1. Title and authors

The full title of the article contained within this sub-section is:

“3D-printed bolus using flexible filament materials - a clinical case study for radiotherapy treatment to the nasal cavity”

The primary author of this article is James Burnley, with advice and contribution from Gerry Lowe, Catherine Lemon, Andrei Caraman, Tom Hague and Geoff Budgell.

3.3.2. Abstract

3D-printing has been shown to be an effective means of manufacture of custom-made devices for use in external beam radiotherapy, particularly as bolus, designed to increase dose to the skin surface. Whilst offering several advantages over current commercially available bolus materials, 3D-printed bolus is often produced using rigid thermo-plastics, notably acrylonitrile butadiene styrene (ABS). Rigid bolus can be difficult to use, uncomfortable for the patient and provides little contingency for anatomical change over a typical treatment period. In this case study, a custom bolus was designed to fill a void in the face of a patient undergoing radical radiotherapy treatment to the nasal cavity. The bolus was 3D-printed using NinjaFlex, flexible 3D-printer filament and a low-cost, Taz 6 3D-printer. The bolus was manufactured to a good standard, easy to fit, comfortable, and shown to be effective throughout the course of treatment. It is anticipated that this will become standard practice within our department for similar treatment scenarios in the future.

3.3.3. Introduction

Tissue-mimicking bolus may be used during radiotherapy treatment to increase surface dose for superficial or shallow seated tumours where the

skin-sparing effect offered using high-energy (MV) photons can be a disadvantage. Occasionally it can be required to fill voids or cavities within an intended treatment volume to help produce sufficient, homogeneous, and accurately predictable dose throughout. Commercially available bolus is flat and can be difficult to apply to irregular surfaces and within cavities. The resulting air gaps can further reduce surface dose, compromising the accuracy and effectiveness of the intended treatment [87]. It has been suggested that 3D-printing may offer greater efficiency with reduced operational [44] [45] and production costs [46]. It has been demonstrated as an effective means to manufacture accurate individualised bolus in a range of materials, although these are almost exclusively rigid plastics, notably ABS [52] [46] and PLA [45] [46]. With the recent availability of commercially available flexible materials (e.g. MakerBot, NinjaFlex, Recreus) there may be opportunity to improve the patient's anatomical compliance and comfort [47]. Flexible plastics have been used to 3D-print brachytherapy surface applicators with good geometrical reproducibility and with only small (<3 mm) air gaps observed between the applicator and skin surface following assessment of CT imaging of the applicator in-situ [73].

The purpose of this study was to investigate the use of a novel, flexible plastic to 3D-print an individualised bolus for a patient undergoing radiotherapy following removal of a nasal cavity tumour and to discuss

implications for its use clinically. The increased malleability afforded by such materials may help reduce any potential air gaps that may otherwise manifest over a course of treatment and which would be difficult to remedy using rigid plastic bolus without the need for continuous re-design and re-printing. For tender, hard to reach areas or whenever in direct contact with the skin, flexible bolus may also offer increased patient comfort [51].

3.3.4. Materials and Methods

Case Study

A 69-year old male was referred for adjuvant 3D conformal radiotherapy following surgical removal of a tumour of the nasal cavity. The patient was prescribed a total dose of 65 Gy to be delivered in thirty fractions over a course of six weeks. Following surgery, the patient was provided with a nose prosthesis. It was determined that the prosthesis would be removed during treatment to allow for placement of bolus material within an internal cavity in effort to improve dose conformity. Conventionally, paraffin gauze or wax may be used as bolus, but with internal cavities comes an increased risk of infection and it is often difficult to achieve dosimetrically accurate and reproducible conditions. Within the department, recent developments using 3D-printed bolus and flexible filament materials suggested they may offer a viable alternative to such scenarios and it was agreed to plan with a single

piece of 3D-printed bolus in the knowledge that gauze was readily available if required.

Bolus Design

Initial bolus design was made within the Eclipse (Varian Medical Systems, Inc, Palo Alto, CA) treatment planning system. First the patient's skin was outlined using the auto segmentation tool and further manual adjustment made about the nasal cavity where auto segmentation between the skin and air had failed. A clinician outlined the clinical target volume (CTV) which was subsequently expanded isotopically by 3 mm to create a planning target volume (PTV). A bolus structure was created and contoured such that it covered any air within the nasal cavity proximal to the PTV and level to the skin surface. The skin contour was used to ensure good fit to the bolus within the cavity by subtracting any areas of overlap between it and the bolus using a boolean operation. This was done using an additional 1 mm margin to ensure the fit would not be so tight as to render it difficult to position and remove. Any areas of significant contour change were manually smoothed out and where necessary, re-shaped to increase the likelihood of the printed bolus being successfully positioned within the patient. A small amount of additional bolus was contoured laterally on the surface of the skin to provide means to comfortably remove the bolus once treatment had been completed.

This initial design was exported from the TPS as a DICOM structure, this was then converted to an Stereolithography (STL) file type using the open-source 3DSlicer software (<http://www.slicer.org>). The model was then smoothed and a small volume cut away so as to provide a large, continuous surface area to help maintain good adhesion of the bolus to the print bed. These operations were carried out using MeshMixer modelling software (Autodesk Inc. California, U.S.A.). This final bolus design was exported as STL to the open-source slicing application, Cura (Ultimaker, Utrecht, Netherlands). Cura is used to slice the 3D designs into thin layers and provide instructions specific to the 3D-printer and material in use in the form of G-code. The G-code was uploaded to the printer which was controlled via a Raspberry Pi (Raspberry Pi Foundation, Cambridge, U.K.) running the OctoPrint software (<http://www.octoprint.org>). This entire process is detailed schematically in Figure 25 and it is estimated took approximately one hour to complete.

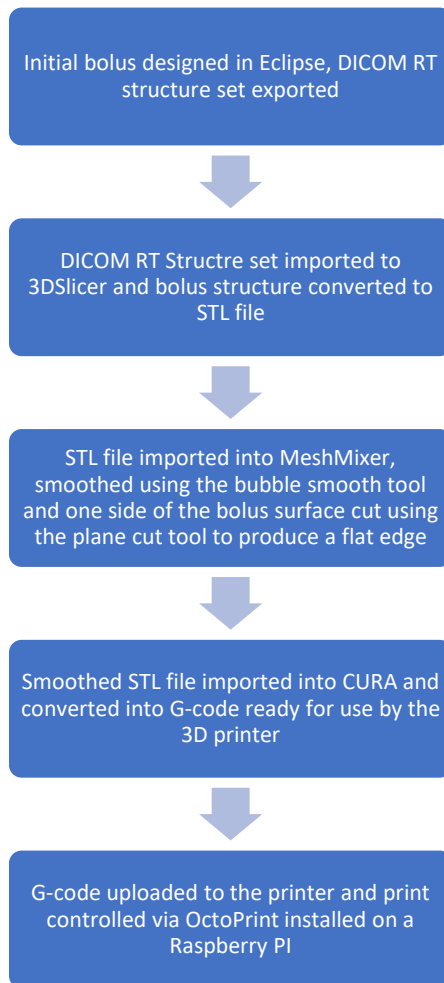


Figure 25 Clinical workflow for production a custom 3D-printed bolus

Three-Dimensional Printing

For this study we used a Lulzbot® Taz 6 (Aleph Objects Inc. Colorado, U.S.A.) fused-deposition modelling (FDM) type printer configured with the FlexyDually (Version 2) extruder (Aleph Objects Inc. Colorado, U.S.A.). The FlexyDually consists of dual extruders mounted on a single carriage, with the ability to print using both rigid and flexible materials at temperatures of up to 300°C. The filament used was NinjaFlex by NinjaTek (Feener Inc., U.S.A.)

and was 3 mm in diameter. A wide range of settings can be configured within the slicing application some of which can have a significant effect on the suitability of the printed bolus for use as a tissue-mimicking material. A selection of the specific printer settings used is detailed in Table 12.

Parameter	Setting
Bed Temperature	40°C
Extruder Temperature	225°C
Layer Height	0.39 mm
Extrusion Width	0.6 mm
Print Speed	20 mm/s
Infill pattern	Cubic
Infill percentage	80%

Table 12 Sample of settings used for printing in NinjaFlex using the Taz 6 3D-printer

Previous studies have highlighted the effects of changing infill percentage and the importance of establishing correspondence between it and the measured Hounsfield Unit consequently used by the TPS [47]. This has been done for the NinjaFlex material printed on our Taz 6 printer and is detailed in a separate study (see section 3.2). Although printing at higher infill percentage can produce a more water equivalent bolus, it is inevitably less flexible. Given the TPS can accurately compensate for this, a compromise between the water equivalence and flexibility of the material was made. Ensuring that the printed material remains attached to the print bed can be difficult and is vital to successfully completing prints. The Lulzbot® Taz 6 has

a heated print bed with a Polyetherimide (PEI) surface, designed to maximise surface adhesion. In practice, we found this to be inadequate unless in combination with a thin layer of water-soluble adhesive (Pritt, Dusseldorf, Germany). The final print took around one hour to complete. The patient G-code file was stored for the duration of the treatment so that additional copies could quickly be fabricated should the original become lost, damaged or contaminated. The bolus was labelled for identification, orientation and wrapped in cling film in an effort to maintain a microbial barrier between it and the patient. This was removed and replaced for each use. A copy of the final printed bolus is shown in Figure 26.



Figure 26 A 3D-printed copy of the final bolus design

Quality Assurance

To ascertain the geometrical accuracy of the printed bolus versus the intended design, a CT scan of the bolus at 2 mm slice thickness was acquired. The scan was fused to the patient's planning CT scan and orientated such that the position of the printed bolus most closely approximated the position of the bolus in the treatment plan. Using a lung tissue window and level setting, a visual check of agreement could be made. A visual check of structural integrity was also carried out, the bolus was inspected for any gaps, sharp edges and areas of excess material.

Treatment planning

For the purposes of planning, the bolus structure was considered as if it were tissue but with its density overridden to allow calculations to take into account the non-water equivalence of the material. The actual override used was established when commissioning the material for clinical use and is detailed in previous work (see section 3.2). For comparison, a copy of the final plan was re-calculated without override. No attempt was made to optimise the plan without the bolus in the place. The bolus structure was included as part of the PTV for the purpose of plan optimisation, however, for reporting of dose statistics, the original PTV structure was used, cropped 5 mm from skin as this prevented a poor plan being obscured by good dose

coverage to the bolus. Due to the proximity of the PTV to both the optic nerve and globe, they were cropped from the PTV with a margin of 8 mm. Additionally, as the CTV extended to the surface of the skin anteriorly, a virtual bolus structure was used to ensure an appropriate treatment margin was maintained in all directions. The final planned monitor units were calculated assuming that only the flexible bolus filling the cavity would be used.

3.3.5. Results and Discussion

Quality Assurance

The final bolus printed without incident and was found to be a satisfactory reproduction of the intended design with a maximum discrepancy at any one location observed as approximately 2 mm, see Figure 27. The CT scan revealed no obvious defects or voids. Small air gaps resulting from the reduced infill pattern could be seen, as could the increased wall thickness. CT number within the bolus varied from approximately -500 to -80. For reasons discussed previously, an override of -394 was used for treatment planning, corresponding to an electron density (relative to water) of 0.61.

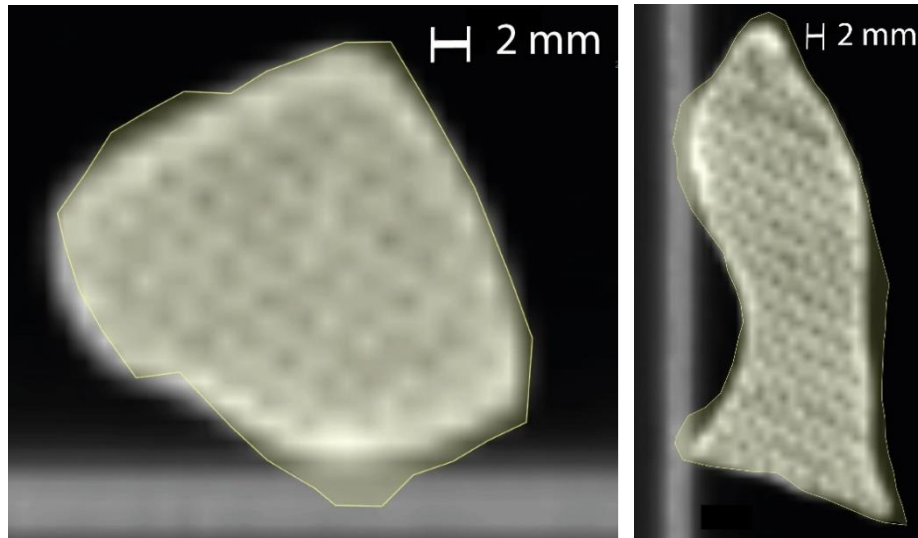


Figure 27 Fused CT images of the printed bolus versus intended bolus design (yellow). A maximum discrepancy at any point was observed to be approximately 2 mm as seen in the image (Right)

Treatment planning and dosimetry

A final plan was produced that satisfied all the agreed clinical objectives for the optimal PTV and any proximal organs at risk. A dose volume histogram revealed that 97.0% of the PTV was planned to receive at least 95% of the prescribed dose. Dose was relatively homogenous throughout the PTV with no significant areas of increased dose observed and a maximum point dose of 107.6% of the prescription dose. Due to the size, shape and positional uncertainty attributed to using paraffin gauze, it was not possible to draw direct comparison. For information, the plan was recalculated with the bolus override removed, the corresponding distribution is shown, compared to the planned treatment in Figure 28.

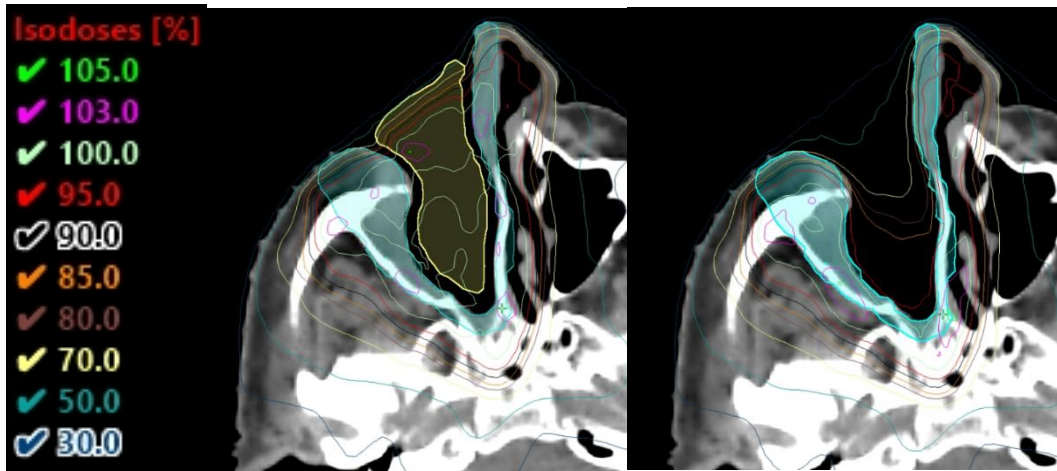


Figure 28 Sample dose distributions of the clinical plan (Left) and the plan recalculated without bolus (Right) The clinical target volume is shaded cyan and the bolus yellow

Without bolus the volume of PTV receiving at least 95% of the prescription dose dropped to 84.6%. A dose volume histogram comparing PTV coverage for both the Bolus and no-bolus plans is shown in Figure 29.

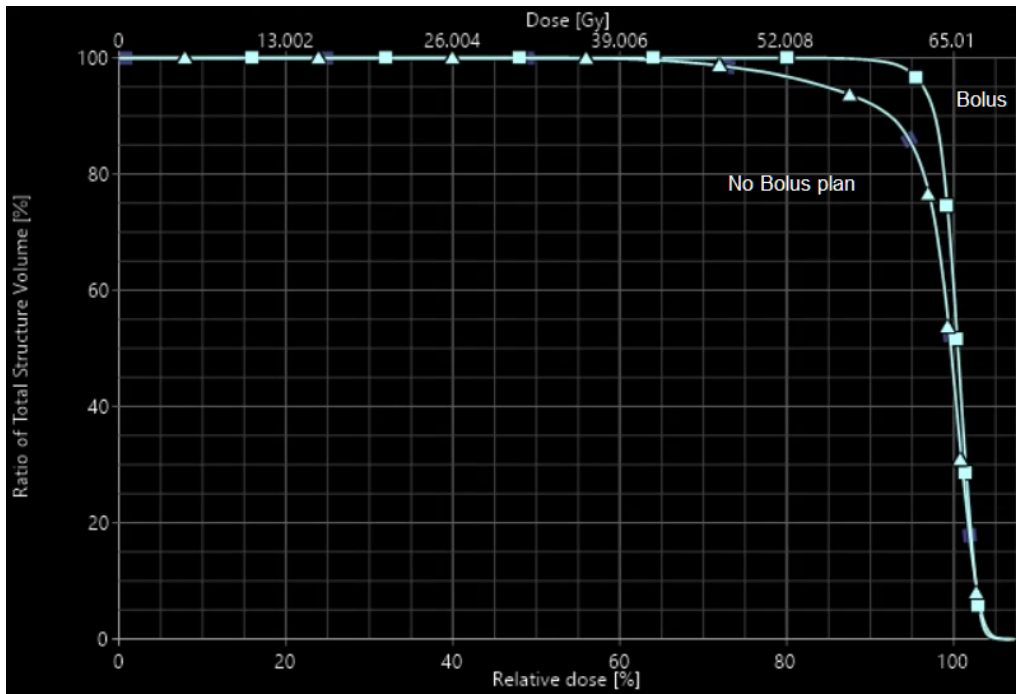


Figure 29 Dose volume histogram comparing calculated PTV dose for both the bolus and no-bolus plans

Patient Fit and Long-term Stability

The patient was informed of the need for bolus in advance and consented to insert it directly themselves. The patient reported no concerns and fitted the bolus in significantly less time than it is anticipated would have taken the treatment radiographers using paraffin gauze. Internal fit was assessed via CBCT images acquired prior to treatment delivery. The bolus was clear to see and could easily be compared to the bolus structure exported from the TPS. No significant air gaps (>5 mm) were observed. Following treatment, the bolus was easily removed and the protective cover disposed of. The bolus was securely stored for subsequent fractions, an additional bolus was printed and checked ready for use to cover any potential future loss, damage or contamination.

Using CBCT, position and fit could be assessed throughout treatment. No further adaptation to the bolus was required and the patient completed treatment without concern. Position and fit on the first and final days of treatment are compared using CBCT images in Figure 30.

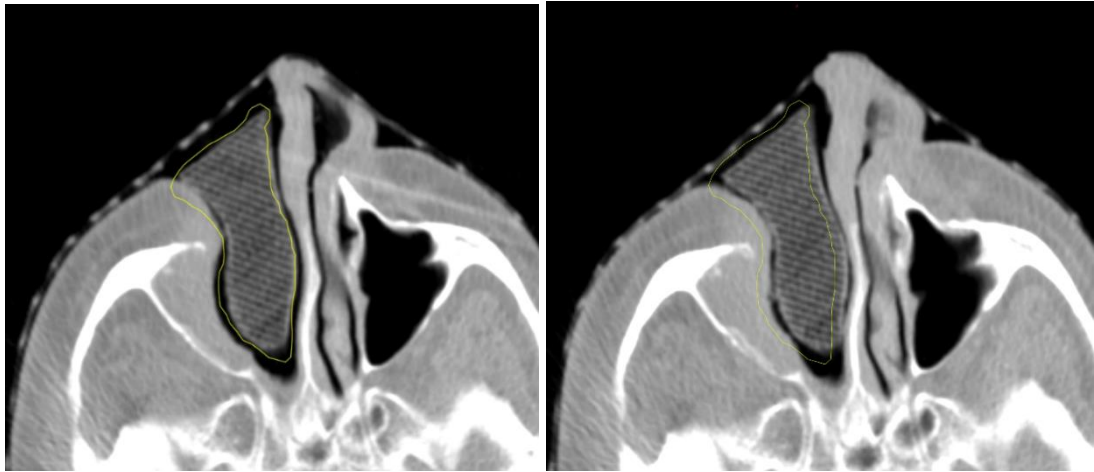


Figure 30 Bolus position and fit assessed via CBCT on #1 (Left) and #30 (Right). The yellow contour represents the planned bolus contour and position

3.3.6. Discussion

In this study we designed and manufactured a custom flexible bolus plug using a 3D-printer and showed it to be suitable for use within a patient undergoing radiotherapy to the nasal cavity. Despite its flexibility, the bolus was not seen to lose shape or dimension over the course of treatment.

Traditionally filling such cavities with paraffin gauze would likely result in significantly greater setup uncertainty, take more time to position, may be uncomfortable to the patient and possess an increased risk of infection and/or loss. Similar studies using rigid plastics have reported patient discomfort with the hardness of the material often cited as the cause [55]. In order to achieve a comfortable fit, the bolus was cropped 1 mm from the skin surface, potentially giving rise to corresponding air gaps as were observed

via CBCT imaging. Provided the size and shape of the bolus renders it feasible, it may be prudent to print additional non-cropped and 2 mm cropped versions so that a 'best fit' can be found, perhaps even on a day-to-day basis. Although it was not required in this case, printing additional copies of the bolus should be considered as, depending on the size of the bolus, print times will typically run into hours. Having a clean copy in case of loss or contamination can help prevent treatment delays at the expense of the additional time that will be required to print and QA each bolus.

Quality Assurance and Clinical Considerations

A prior risk assessment revealed a moderate risk of dosimetric difference between the plan and treatment due to geometrical variation in the printed bolus. Due to the nature of manufacture, FDM style 3D-printing does not usually result in internal defects such as air gaps or inconsistencies without becoming obvious that the entire print has failed. For this reason, we do not routinely CT scan bolus prior to treatment when using ABS. Instead a visual check is performed and physical dimensions are checked against the intended bolus design. Although the bolus in this study printed without incident, our experience to date using NinjaFlex suggested a more vigorous approach to QA may be required. Where a discrepancy is observed or the bolus is difficult to measure, a CT scan may be performed and the resulting

image registered and compared to the bolus structure within the planning CT. Particularly when printing large bolus over extended periods of time, we frequently observed reduction in flow rate of material resulting in a spongy hollow bolus which was not immediately obvious from the external structure alone. It is anticipated that some of this risk may be alleviated through further optimisation of printing parameters and manufacture of a printer enclosure to help maintain consistent temperatures within the printing environment. Additionally, the bolus presented a moderate risk of infection. Printed surfaces were rough, difficult to clean and sterilise. The use of plastic wrap in an effort to maintain sanitary conditions replicates existing methods made using non-sterile commercial bolus and has been suggested elsewhere [46]. Ideally, the bolus itself would be sterile and chemically stable for use within the body. This should be further investigated to ensure the risks of infection are kept to a minimum.

Cost and Time Implications

Flexible 3D-printer filaments can be significantly more expensive than rigid types. At the time of writing, NinjaFlex could be purchased for approximately £60/kg, ABS is typically one third of this cost. Bolus is usually small and so despite material cost, it is not anticipated that the design and manufacture of a custom 3D bolus would cost significantly more than an

equivalent use of gauze over a course of a typical treatment. Considering the cost of the equipment, consumables and staff time for design, production and QA, it was estimated that design and manufacturer of a complex 3D-printed bolus costs approximately £180 per patient. A comparable conventional bolus made using wax sheets or paraffin gauze was estimated to cost £120. The time taken to design and prepare the bolus for printing was not found to be overly burdening although it should be appreciated that the department already has extensive experience designing and 3D-printing bolus using rigid plastics. A significant disadvantage of using Ninjaflex over ABS is the speed at which it can be printed. Equivalent bolus made using ABS could be printed in a third of the time. Bolus is typically small and the printing process almost entirely automated and so unless large numbers of bolus are to be produced in any one day, it is not envisaged that this would have significant effect on the majority of clinical departments. A summary of

estimated time and costs for each of the discussed materials and methods are presented in Table 13.

	ABS	NinjaFlex	Conventional
Staff time	1h	1h	1h30
Production Time	4h	6h	1h30
Total Cost	£90	£180	£120

Table 13 Approximate costs of 3D-printed bolus using ABS and NinjaFlex versus a conventionally produced bolus using gauze/wax

3.3.7. Conclusion

A 3D-printed bolus was successfully designed to accurately and reproducibly fill an irregular cavity within the nasal cavity of a patient using NinjaFlex flexible filament material. A single piece of bolus was used and was shown to be effective, easy to position and comfortable throughout the course of the six-week treatment. It is anticipated that using customised 3D-printed bolus in this way may be superior to using existing commercially available materials due to the increased reproducibility and the reduction in air gaps between the patient's internal surface and the bolus material. Maintaining sterility of the bolus is of potential concern, particularly as the surface of the printed bolus can be rough and uneven. It is envisaged that more appropriate methods of forming a barrier between the bolus and the patient may exist and should be investigated. Additionally, newer, flexible

3D-printer filaments may be developed which are easier to clean and maintain. As a proof of concept, the study was useful and follows on from additional work characterising flexible 3D-printer filament materials and the commissioning of rigid 3D-printed bolus for head and neck patients within the department.

Chapter 4 - Critical Appraisal

The following chapter has been compiled following completion of the written research and is intended to detail a critical appraisal of the work carried out by the author including any limitations of the research and implications it may have to clinical practice.

4.1. Strengths and Weaknesses

4.1.1. Low Energy X-rays and Electrons

Whilst sufficiently detailed to facilitate clinical implementation, material characterisation has been performed only for high energy photons (6 and 10 MV). Whilst it could be argued that superficial treatments using low energy x-rays do not typically require use of bolus, treatments using electrons in the megavoltage range do commonly use bolus material to ensure sufficient surface dose, to modulate dose distributions and to maintain homogeneity. Whilst the radiological properties of both rigid and flexible thermoplastics in kilovoltage beams has been investigated [10] this did not extend to the materials discussed here and no evidence was found of similar studies made using electrons. Measurements of attenuation and surface dose using electron beams have been made by the author for ABS,

PLA, NinjaFlex and Cheetah materials. Although it has been commissioned for clinical use, flexible, 3D-printed electron bolus is not commonly used at the Mount Vernon Cancer Centre, primarily because patients undergoing treatment with electrons are not routinely CT scanned and there is currently no alternative means to obtain the volumetric surface information necessary to produce well-fitting bolus. This work was not presented here in the interest of time and continuity but was communicated at the clinical study day and continued research and publication would certainly be of benefit to existing work.

4.1.2. Custom MATLAB Code

The custom MATLAB code developed to aid production of brachytherapy surface applicators performed well and was successfully evaluated for a range of clinical scenarios not presented here, including a scalp and nose. It has not been described in significant detail, without which, it is unlikely to benefit from widespread distribution amongst the radiotherapy research community. Further development is required to better facilitate manual adjustments, as were required when significant contour change resulted in unusable source channels as detailed previously. Better integration with various TPS would be beneficial and could easily be achieved with the support of their respective manufacturers. During the research, it became

apparent that a commercial solution (Adaptiv) was under development and is now available for purchase [77]. A full evaluation of this, with comparison to the in-house solution used here, would have been useful but was not possible due to financial constraints and the timing of its release.

4.2. Limitations

Unlike most commonly encountered radiotherapy equipment, there is an extensive range of 3D-printers, produced by numerous manufacturers. It is anticipated that methods, advice and results presented in this thesis may be applicable to printers other than the Taz 6 but this is uncertain. Also, non-FDM printers typically use alternate materials, requiring their own investigation, although some preliminary work on flexible printed materials using non-FDM printers exists in the literature already [15]. Ideally, comparison would be made with alternative printers and filament batches but this has not been possible and so care should be taken when applying any research findings to own clinical practice.

4.3. Implications to Clinical Practice

This thesis has demonstrated that 3D-printing can be successfully utilised in radiotherapy with the potential to replace and, improve on, existing manufacturing processes. For radiotherapy bolus, it is envisaged that all but

the simplest designs would benefit from the level of customisation that 3D-printing can offer. If an efficient and user-friendly workflow between bolus design and print can be established, it is envisaged that most patient bolus would be 3D-printed. Over time, subtle changes to bolus design may become apparent as increased consideration is made to facilitate printing and to utilise the increased flexibility it offers. For example, the inclusion of at least one large sided surface and a reduction in the use of square or rectangular shaped bolus. Such changes are likely to be slight and gradual with little implication to staff training or resource. The manufacturing process however is likely to see significant change as manual labour is replaced by semi-automated print processes that can be configured and monitored remotely at any time.

The process of 3D-printing brachytherapy applicators differs significantly from existing, conventional methods typically carried out by technicians or radiographers. With an emphasis on design, requiring use of limited commercially available or in-house software solutions, this role may best suit scientific staff or engineers with knowledge of CAD and/or programming. Over time this will likely result in a loss of experience and expertise of manual fabrication of such devices.

As a novel technology and with uncertainties surrounding the long-term stability of printed filament materials, it is likely that additional QA will be

required, though this is not expected to be onerous and methods can be based on use of existing equipment available in most departments and as has been described previously. Geometrical variation throughout treatment is not thought likely. Whilst flexible printer materials can be used to compensate for slight anatomical variation, gross changes will require re-design and re-print, and this is to be expected in some cases.

For 3D-prints intended for use for humans, it is likely that classification and regulatory compliance as medical devices would be required. In the U.K. and European Union, specific exemptions exist for those devices intended for the sole use of an individual patient and made in accordance to a written prescription or design and to devices intended for use within the same health institution as in which they were made [86]. Whilst applying such exemptions precludes the need for CE marking, elements of the regulations still apply. Accordingly, 3D-printed devices should meet certain safety and performance requirements and their manufacture covered by a quality management system which includes written protocols, training procedures and records as well as mechanism to monitor and improve results. As a 3D-printer is not intended for use with patients it is not likely to be considered a medical device in itself.

Finally, with an anticipated increase in use of 3D-printing comes detrimental environmental implication. Recycling of thermoplastics is generally widely

available and so, notwithstanding the potential obstacle of sterilisation, such effects may be mitigated. Many of the existing bolus materials cannot safely and suitably be reused and so 3D-printing may offer better long-term sustainability.

4.4. Barriers to Implementation

Despite widespread interest in 3D-printing, evident in the literature and through attendance of the clinical study day, implementation has been slow. One reason for this may be a lack of printing facilities, with the cost of a 3D-printer and commercial software in particular, requiring justification and a proportionate amount of financial outlay. Use of open-source hardware and software can reduce costs significantly but there is potentially fear that, by doing so, 3D-printing will require an excess of knowledge and a significant amount of time to commission. The Taz-6 and NinjaFlex filament used throughout this work took approximately one year to fully implement at the Mount Vernon Cancer Centre. So, whilst this can be true, there is little evidence to support the idea that commercial solutions offer significant improvement. Indeed, many commercial solutions are built upon open-source hardware and utilise custom versions of open-source software. Similarly, use of commercial software does not mitigate legal responsibilities that may be due when manufacturing potential medical devices using 3D-

printers, these should be no less onerous than those employed for existing custom made, patient intended equipment. Regardless, there is little doubt that uncertainty surrounding the use and classification of 3D-printed objects as medical devices also presents as considerable challenge to anyone intending to implement 3D-printing of patient specific equipment into their own practice.

Chapter 5 – Conclusion

5.1. Summary of Findings

This thesis evaluated use of 3D-printing and the suitability of flexible printer filament materials within clinical radiotherapy practice. Following a review of the existing research literature and the manufacturer of a brachytherapy surface applicator using 3D-printed rigid plastic, further research requirements into use of novel, flexible filaments were identified, conducted and presented as both scientific and clinical case studies. 3D-printing was shown to be an effective and accurate alternative to existing manufacturing techniques for producing highly complex objects with the ability to conform well to irregular surfaces such as those found on the skin. For patients undergoing radiotherapy, where CT images are typically acquired for the purpose of radiotherapy planning, design of such objects can be based on segmentation of anatomy from imaging information alone. This has the potential to greatly improve the overall patient experience by removing the need for a plaster or thermoplastic impression, subsequently reducing the number of hospital appointments. A brachytherapy surface applicator was designed in this way containing a series of hollow guides, positioned using an in-house developed MATLAB program and various open-source software

via a relatively automated process. 3D-printed objects printed using flexible filaments such as the commercially available NinjaFlex or Cheetah can offer further enhancement by being more comfortable to position and with the ability to adapt to subtle changes to a patients surface contour over a typical course of treatment.

An additional study investigated the dosimetric characterisation of Ninjaflex and Cheetah materials and a comparison made to both a commonly used rigid plastic and water. Despite doubts over their water equivalence, their use as bolus may be considered provided appropriate accommodation for this is made within the TPS. Recommendations for commissioning flexible printer materials including specific printer settings have been detailed as well as advice on interpretation and application of the relevant medical devices regulations.

Finally, a clinical case study demonstrated the effectiveness of a flexible 3D-printed bolus designed using CT data and used to fill an irregular cavity within the nasal cavity of a patient being treated following surgical removal of a malignant tumour. The bolus allowed for near ideal planning conditions with minimal amounts of air present within the intended treatment volume and was easily and relatively comfortably positioned by the patient themselves over a course of a six-week treatment. In-vivo imaging using

CBCT verified day to day placement of the bolus within the cavity and ensured that the overall integrity of the bolus had been maintained.

5.2. Research Aims Accomplished

The aim of the thesis was primarily to support and facilitate more widespread use of 3D-printing in radiotherapy through investigation into the characterisation, commissioning and use of flexible 3D-printer filament materials. Through presentation of a series of clinical case studies, it was possible to detail the complete process of commissioning and implementation, which it is anticipated, could easily be applied to individual practice. When compared to current practices, detailed throughout various literature, the hypothesis that 3D-printing using flexible filament materials can result in efficient, accurate and comfortable custom-made devices is likely to be true. Further improvements are expected to be both desirable and achievable and are discussed in the subsequent section. The contribution 3D-printing has to the overall patient experience and treatment outcome is less clear without additional evaluation and follow-up. With respect to the secondary objectives of the thesis, open-source software has been used to good effect throughout and can be recommended. Legal issues have been considered and interpreted with a discussion present throughout the work and summarised during presentation at the clinical study day held in 2019.

5.3. Areas for Future Work

Despite successful implementation of 3D-printing within radiotherapy, evident within the existing literature and the results of clinical use of flexible filament materials detailed within this thesis, uncertainties remain and are potentially limiting more widespread uptake. Several areas have been identified that would benefit from further research/development to better alleviate such concerns and build upon initial successes.

5.3.1. Software Workflow and Clinical Integration

Development of 3D-printing equipment and any associated software has, to date, been carried out with little consideration for the demands and implications of a typical radiotherapy department. FDM style printing is likely driven by the hobbyist and small business market with a primary focus on cost. Whilst this can be an advantage, it has resulted in most low-cost printers being based upon open-source software solutions which are often built for more general use and can have steep learning curves. Integration with existing radiotherapy systems can be limited and often multiple software solutions are required to create, convert and process information to a suitable format for printing. It is hoped that, as 3D-printing becomes more commonplace within radiotherapy, specific software solutions, whether open

source or not, will be developed that will help improve workflow, efficiency, and usability of the process.

For all aspects of 3D-printing intended for use for human beings in the U.K. the current medical devices regulations apply [86]. These regulations are designed to manage, monitor and ensure safety of manufactured devices. Whilst specific exemptions apply to those devices intended for use in the same institution in which they are made and for certain custom-made devices, the medical devices regulations provide the necessary framework for their management within a hospital environment. An appropriate quality management system should be designed to cover all aspects of a 3D-printing service and safety and performance checks of both equipment and printed devices carried out at appropriate intervals.

5.3.2. Acquisition of Volumetric Information

The majority of radiotherapy patients undergo some form of imaging as part of the treatment planning process and this may be used to obtain the geometrical information necessary to produce patient-specific, well-fitted devices. Some treatments do not require three-dimensional imaging, for example when treating very superficial lesions or for certain palliative treatments. In such cases the additional risks attributed to the imaging procedure, i.e. additional radiation dose, must be justified. Alternative

methods have been proposed using a series of photographs [88]. Such solutions are quick, convenient, non-invasive and have the potential to be applied to most patients. The effectiveness of using imaging modalities other than CT is also not well understood and with increasing use of MRI and CBCT further assurances should be sought. MRI in particular may facilitate better fitting bolus due to its superior representation of subcutaneous tissue, however, it is more prone to motion artefacts and geometric distortion when compared to CT imaging.

5.3.3. Bio-compatibility and Sterilisation

With the exception of the PC-ISO material, which is not currently available for use in FDM style printers, the 3D-printed filaments discussed in this thesis have no formal recognition of biocompatibility. Until this is achieved, or alternative approved materials commissioned, a physical barrier is likely to be required between the printed filament and the patient surface. To minimise risk to the patient, ideally, printed objects should also be sterilisable. When not using a physical barrier, un-sterilised printed objects may possess a significant infection risk, particularly as printed surfaces can be rough and uneven when using FDM techniques. Using existing, approved materials, engineered using 3D-printed moulds or templates has been suggested as a potential workaround [88] but this results in waste material

and the potential introduction of inaccuracies manifested from one design to the next. Methods used to seal and sterilise similar devices may exist and prove just as applicable to 3D-printed materials and should be investigated.

5.3.4. Long Term Stability

Discussed in this thesis is predominantly single course use, patient-specific 3D-printed devices. In theory, commercial, universal design devices consisting of two-dimensional sheets of material could be reproduced/replaced using printed flexible filaments. Whilst consideration has been made for the short-term stability of flexible printer materials, further assessment of its long-term stability, beyond the typical timeframe of a radiotherapy course would therefore be of benefit. Dosimetric, as well as geometric stability should be verified for periods at least comparable to the lifetime of commercially available alternatives. Under normal conditions most printed materials can be considered to be chemically stable but the effects of prolonged radiation exposure may be less certain and chemical or mechanical sterilisation techniques can carry the potential to damage or modify individual material properties sufficient to effect its intended performance as a medical device.

5.4.Expectations for the Future

With 3D-printing equipment becoming ever more accessible and increased demand for individualised treatments, more widespread uptake of 3D-printing within radiotherapy is expected. Particularly for those centres with existing mould room facilities, a strong case can be made for the purchase of a low-cost, FDM-style printer. With the relevant expertise, custom designs may be printed and tested relatively quickly and at the same location for which they are intended to be used. For smaller centres with potentially limiting budgets or with a lack of relevant expertise, a more viable option may be the outsourcing of a design to a specialist 3D-printing provider who could, in theory, provide a printed design in a wide range of materials. Such services currently exist for commercial purposes and notwithstanding the medico-legal factors associated with the transfer of patient-sensitive data and the production of devices intended for medical use, could readily be made available for the healthcare industry.

5.5.Recommendations

In conclusion, the following recommendations are made with respect to 3D-printing for radiotherapy and following the work presented in this thesis:

- 3D-printing using low-cost, FDM-style printers should be considered as a viable, accurate and efficient means to manufacture patient specific devices in a range of thermoplastic materials.
- Widely available flexible filament materials cannot be considered as water equivalent as their rigid counterparts, but this can be easily mitigated for by way of a density override within the TPS. An appropriate override value should be determined based on individual practice and equipment.
- Printing flexible filaments at high infill rates (>80%) can produce strong but stiff objects and as such is not recommended when anything other than slight flexibility is required. Infill rate has a significant effect on density and so must also be assessed and appropriately compensated for in the TPS.
- Low infill rates can be used when water equivalence is not required or is significantly disproportionate to other uncertainties (i.e. positioning). Use of lower infill rates significantly reduces print time and material cost.
- Until biocompatibility of printed materials can be confirmed and the risks of infection due to contamination satisfactorily mitigated, it is advised that a physical barrier between print and patient is

maintained. This should ideally be done using a thin sheet of biocompatible material, replaced between uses.

- FDM printing requires a strong initial printed layer on which an object can be constructed. Various equipment and methods may be employed to help achieve this. It is recommended that a heated print bed is used in combination with a layer of water-soluble glue and a brim of sacrificial material attached to the objects initial layer to increase its contact area.
- The environment in which a printer is located, particularly ambient temperature, can have a significant effect on achieving successful, reliable and consistent outcomes. Consideration should be made to the physical location of 3D-printing equipment and to use of an enclosure to help maintain a consistent temperature and minimise air drafts.
- Due to the unique nature of the manufacturing process, individual QA of 3D-printed objects is unlikely to be overly cumbersome, with most serious defects/inhomogeneity clearly presenting themselves following manufacture. Flexible printer filaments can be more prone to inhomogeneity than rigid filaments and long-term reproducibility uncertain. A CT scan using moderate resolution can be used to provide sufficient assurance of both geometric and physical attributes of the printed object and is recommended.

- 3D-printing technologies are not currently well supported by most radiotherapy software and equipment vendors and there are limited commercially solutions presently available. Use of open-source or in-house software may be required and should be carefully considered, including any necessary medical-legal requirements.

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Appendices

Appendix 1 – Details of AMBS A units, Medical Physics B units, Generic B units and Section C together with assignments

AMBS – A Units		
Unit title	Credits	Assignment wordcount
A1: Professionalism and professional development in the healthcare environment	30	Practice paper – 2000 words A1 – assignment 1 – 1500 words A1 – assignment 2 – 4000 words
A2: Theoretical foundations of leadership	20	A2 – assignment 1 – 3000 words A2 – assignment 2 – 3000 words
A3: Personal and professional development to enhance performance	30	A3 – assignment 1 – 1500 words A3 – assignment 2 – 4000 words
A4: Leadership and quality improvement in the clinical and scientific environment	20	A4 – assignment 1 – 3000 words A4 – assignment 2 – 3000 words
A5: Research and innovation in health and social care	20	A5 – assignment 1 – 3000 words A5 – assignment 2 – 3000 words



Medical Physics – B Units		
B1: Medical Equipment Management	10	2000 word assignment
B2: Clinical and Scientific Computing	10	2000 word assignment
B3: Dosimetry	10	Group presentation 1500 word assignment
B4: Optimisation in Radiotherapy and Imaging	10	Group presentation 1500 word assignment
B6: Medical statistics in medical physics	10	3000 word assignment
B8: Health technology assessment	10	3000 word assignment
B9: Clinical applications of medical imaging technologies in radiotherapy physics	20	Group presentation 2000 word assignment
B10a: Advanced Radiobiology	10	Virtual experiment + 1500 word report
B10c: Novel and Specialised External Beam Radiotherapy	10	1500 word report/piece of evidence for portfolio

B10i: Ionising Radiations Instrumentation Specialisation	10	1500 word report/piece of evidence for portfolio
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Generic B Units		
B5: Contemporary issues in healthcare science	20	1500 word assignment + creative project
B7: Teaching Learning Assessment	20	20 minute group presentation

Section C		
C1: Innovation Project	70	4000-5000 word Literature Review Lay Presentation

Appendix 2 - Innovation proposal - 3D-printing in radiotherapy



Innovation Proposal

3D-PRINTING for Radiotherapy

James Burnley
Mount Vernon Cancer Centre and University of Manchester
February 2018



Executive Summary



Production of customised skin bolus and brachytherapy surface applicators is currently limited to the expertise of the practitioner and is time and resource intensive. Additionally, poor geometrical results can have significant effect on the effectiveness of treatments.



Research suggests 3D-printed bolus using readily available printers and materials can produce a more accurate reproduction of a design with physical and dosimetric characteristics comparable to currently used materials. Better accurately reproduced bolus improves patient comfort and treatment outcome.



Developing from the skin bolus technique, 3D-printed brachytherapy surface applicators have the potential to save significant staff resources and reduce the number of hospital visits required of a patient.

Background

3D-printing is a form of additive manufacturing developed over 30 years ago. It has been in use within a healthcare environment since the early 2000s when it was first used to make custom





prosthesis and implants. With increased accessibility and affordability its practice is unlikely to decline. In healthcare, it is estimated that the 3D printing market will be worth \$6 billion by 2025 in the U.S. alone. Recently the use of 3D-printing technology within radiotherapy has been explored. It suggests it may be a viable alternative to conventional techniques for producing custom bolus material, quality assurance phantoms and brachytherapy applicators saving both staff time and resource whilst producing more accurate, better fitting devices.











Impact of innovation

Long term impact of 3D printing for the two most likely applications within radiotherapy has been considered and is presented below. Short term impact would require commissioning of the 3D printer, staff training and software development. Additionally, changes to patient pathways may need to be considered and implemented prior to any clinical introduction.

Complex Tissue Bolus

	Current	Proposed
Bolus Design	Bolus planned by treatment planning staff with input from clinical oncologist (20 minutes)	No change
Preparation	Electronic request made by planning staff (5 minutes)	Bolus design prepared for printing by planning or dosimetry staff (30 minutes) 
Fabrication	Radiotherapy assistant/clinical technologist to produce using paraffin gauze/wax (1 - 2 hours)	Fully automated print process, some post processing and QA may be required (30 minutes) 
Result	Good for simple geometries, poor for complex often resulting in gaps which can effect efficacy of treatment 	Excellent fit for almost all geometries however complex prints may be prone to failure and require repeat processing
Time Required	1h30 - 4h (Staff) 1h30 - 4h (Production)	1h - 1h30 (Staff) 6h - 24h (Production) 
Costs	approx. £120	approx. £180* (Including cost of printer/software) £100 (Print only)
Key Risks	- Air gaps limit effectiveness of treatment - Material degradation over time	- Lost bolus would require re-printing potentially delaying treatment - Long print times limits capacity (not all patients to benefit)

Brachytherapy Surface Applicators

Applicator Design	Applicator shape and size drawn by physicist based on treatment volume as defined by clinical oncologist. Performed following CT scan of shell (1 - 2 hours)	No wait for CT scan of shell, drawn directly overlaying treatment volume, potential for automation based on target volume definition 
Catheter Placement	Catheter guides manually positioned within proposed applicator (1 - 3 hours)	Catheter guides positioned automatically within proposed applicator based on fixed spacing and standoff from patient surface, some manual adjustments may be required (10-30 minutes) 
Preparation	Patient attends and a plaster impression is made (1-2 hours with further time required for setting) 	No further patient visit required, surface rendering may be established from CT/MRI data
Production of Applicator	Produced manually using thermoplastic shell and combination of wax/paraffin gauze, can require multiple modifications to obtain good, patient visits may be required (1-2 hours) 	Minor technical staff time required for printing preparation (15-30 minutes). Fully automated print process (12-48 hours)
Finishing	Minor modifications may be made with patient present, major redesigns timely but unlikely to involve starting from scratch (30-60 minutes)	Removal of support structures and final preparation of print (including QA) may be required (30-60 minutes). Failed prints would need to be reprinted (12-48 hours). Patient unlikely to be required once technique established 
Result	Acceptable standard in most cases but setup can be difficult to reproduce resulting in significant treatment uncertainties	Stable, reproducible and better fitting applicator. Increased patient comfort and clinical outcomes 
Time Required	5h - 10h (Staff) 15h - 53h (Production) 	1h30 - 2h30 (Staff) 12h - 48h (Production)
Cost	Approx. £400	Approx. £250* (Including cost of printer/software) £170 (Print only) 
Key Risks	- Treatment uncertainties due to placement and reproducibility - Potential risk of source blockage - Infection control risk	- Failed prints requiring reprint may delay treatment - Use of materials not approved for medical use

*3D-Printer costs include cost of printer and software spread over 3 years and assumes 1 patient per week

3D Printing in Radiotherapy

Potential Barriers to implementation

A number of factors have been identified as potential barriers to implementation of 3D-printing within radiotherapy. To minimise additional costs, open source software will be used wherever possible. Where open source solutions do not exist or their use has significant impact on clinical workflow, 'in-house' software solutions will be developed. Uncertainties surround the use of 3D-printed devices for medical use and recent changes to the Medical Device Regulations (MDR) must be monitored. It is anticipated however, that any changes brought upon by the MDR would also apply to existing methods 3D-printing potentially replaces although these are currently approved as medical devices.



Lack of volumetric (surface) data for certain subset of patients



Disruptive workflow



Use of open source or commercially expensive software solutions



Legal Issues - Medical Device Regulations

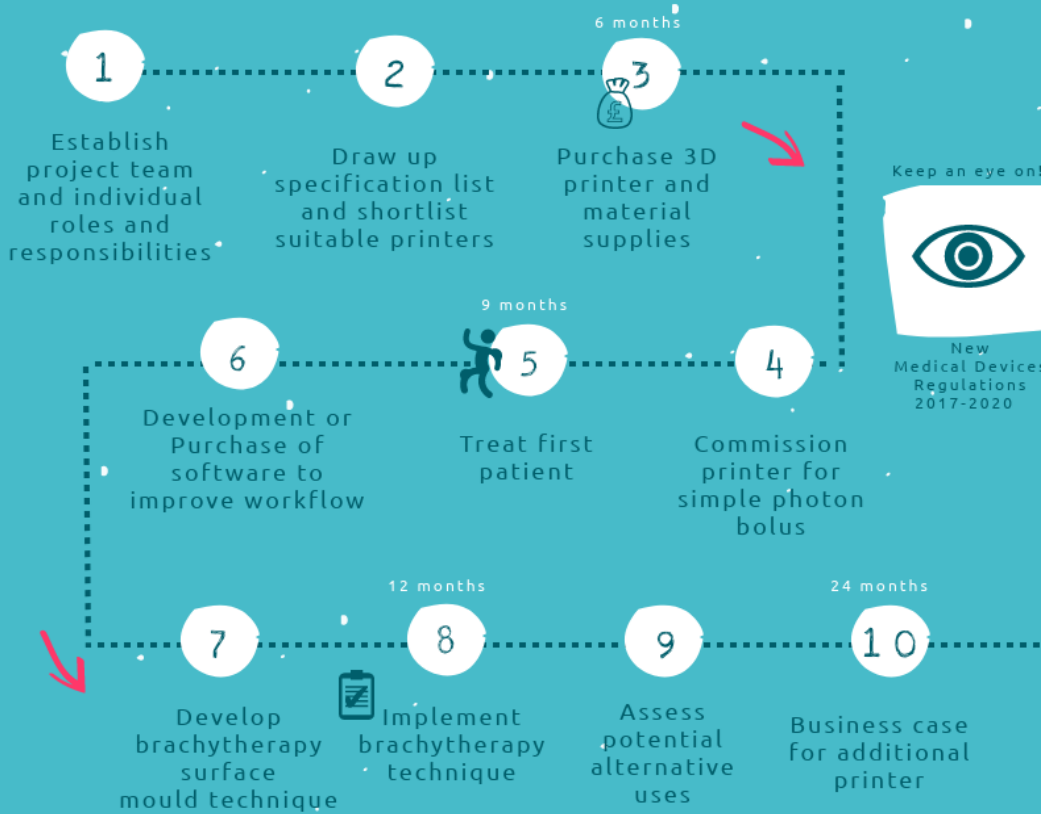


Lengthy commissioning process



Lack of experience, steep learning curve

IMPLEMENTATION PLAN



Stakeholder Engagement

- Key stakeholders identified as patients, clinical oncologists, medical physicists, therapeutic radiographers, clinical technologists, bio-engineers and manufacturers
- Clinical staff have been consulted and informed of the potentials and pitfalls of 3D-printing in attempt to establish any unforeseen ideas in support of, or that otherwise disprove, implementation of 3D-printing
- Positive correspondence with manufacturers of radiotherapy software and 3D printing equipment suggest potential for collaboration and revenue generation
- Feedback from patients involved with existing techniques suggest there is considerable room for improvement to existing techniques



Summary and Key Recommendations



Purchase cheap (sub £1000) 3D-printer

Initially utilise 3D-printed bolus for complex surface bolus only



Develop, 'in-house' or with industry support, software solutions to improve workflow (potential opportunity for commercialisation)



Investigate use of 3D printing in brachytherapy

Summary

3D-Printing within radiotherapy offers both an innovative and practical way to address problems with existing manufacturing techniques of complex tissue bolus and brachytherapy applicators. The benefits of bespoke, accurate treatment techniques must be balanced with financial constraint. 3D-printing offers a cost-effective and pragmatic approach to achieving this today and even more so in the future.

Appendix 3 - 3D-Printing in Radiotherapy clinical study day agenda



**3D Printing in
Radiotherapy**
CLINICAL STUDY DAY
17-09-2019

AGENDA

10:00 - 10:30	REGISTRATION & COFFEE
10:30 - 10:40	WELCOME & INTRODUCTION James Burnley, Lead Clinical Scientist
10:40 - 11:00	OVERVIEW OF HARDWARE & SOFTWARE Oliver Shoffren, Superintendent Radiographer
11:00 - 11:20	REVIEW OF 3D PRINTING IN RADIOTHERAPY James Burnley, Lead Clinical Scientist
11:20 - 11:50	PRINTING DICOM STRUCTURES Andrei Caraman, Assistant Physicist
11:50 - 12:30	WORKSHOP Delegates to be split into 3 groups for short tour/demonstrations
12:30 - 13:15	LUNCH
13:15 - 13:30	BRIEF INSIGHT INTO THE ADAPTIIV SOFTWARE Tom Jacques, Xiel
13:30 - 13:50	3D PRINTED BOLUS Victoria Newton, Trainee Clinical Scientist
13:50 - 14:10	3D PRINTED BRACHYTHERAPY SURFACE MOULDS Gerry Lowe, Head of Brachytherapy
14:10 - 14:30	USE OF OPEN SOURCE SOFTWARE Gerry Lowe, Head of Brachytherapy
14:30 - 14:50	MEDICAL DEVICES REGULATIONS James Burnley, Lead Clinical Scientist
14:50 - 15:00	DISCUSSION & CLOSE

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Appendix 4 – Summary of the literature review

References grouped into one of seven categories as indicated by the shading and in the following order: Bolus materials, immobilisation devices/aids, other, review articles, brachytherapy and phantom design.

Author(s)	Year	Country	Hardware	Material	Software	Topic
Fujimoto et al. [75]	2017	Japan	CubePro	ABS	3D Slicer, MeshLab, CubePro	Efficacy of patient-specific photon bolus
Kim et al. [52]	2014	Korea	Fortus 400 mc	ABS	OsiriX MD, 3Ds Max, Insight	Customised 2D printed photon bolus
Robar et al. [53]	2017	Canada	Taz5	PLA	Meshmixer	Study of 3D-printed bolus Vs vinyl sheet
Lukowiak et al. [89]	2017	Poland	Not Specified	ABS	Not specified	Electron bolus for skin lesions of the eye canthi
Ricotti et al. [47]	2017	Italy	HP3DX100	ABS/PLA	TinkerCad	Dosimetric characterisation of 3D-printed bolus for photon radiotherapy
Michiels et al. [69]	2018	Belgium	Not specified	Not specified	Not specified	Patient-specific bolus for range shifter gap reduction in H&N proton therapy

Canters et al. [44]	2016	Holland	Printrobot Metal Plus	PLA	Pinnacle (Python script)	Clinical implementation of patient specific 3D-printed electron bolus for non-melanoma skin cancer
Park et al. [42]	2017	Korea	Stratasys Objet500 Connex3	TangoPlus	Geomagic Design X	Production of malleable 3D-printed custom bolus using a 3D scanner
Burleson et al. [46]	2015	USA	Airwolf XL 3D	ABS/PLA	3D Slicer, MatterControl Pro	Production of 3D-printed patient-specific bolus for radiotherapy
Su et al. [90]	2014	Canada	Replicator 2	PLA	MATLAB	Electron bolus
Kim et al. [45]	2017	Korea	Makerbot Replicator 2/ANATZ	PLA	3D Slicer	Photon bolus
Zou et al. [68]	2015	USA	Makerbot Replicator 2	PLA	p.d. software, MATLAB	Electron bolus and photon compensators
Park et al. [91]	2016	Korea	CubeX	PLA	KISSlicer, MIM maestro, 3D Slicer, Blender	Clinical application of 3D-printed electron bolus
Park et al. [83]	2016	Korea	MEISTER	PLA	3DSlicer, Simplify3D	Photon bolus

Park et al. [55]	2016	Korea	Dimension 1200	ABS	3DSlicer	Photon bolus - case study
Oh et al. [14]	2017	Korea	HP JET Fusion 3D 42000	PLA	MIMICS, 3-matic	Fabrication of patient-customised helmet
Michiels et al. [92]	2016	Belgium	Various	Not specified	Not specified	3D-printed immobilization devices proton therapy - Material characterisation
Fisher et al. [38]	2014	UK	Formiga P110	PA2200	Not specified	Immobilisation shells for H&N IMRT
Laycock et al. [37]	2014	UK	Z-Corps 650, Eden250	VeroWhitePlus	Tomomask	Radiotherapy treatment shells using CT and MRI data
Haefner et al. [39]	2018	Germany	Stratasys Dimension SST1200es	ABS	Creo Parametric, In-house	3D-printed immobilisation masks
Roberge et al. [40]	2018	Canada	Big Builder	PLA	3DSlicer, CATI	Radiotherapy masks moulding using 3D-printed head models
Meyer et al. [43]	2018	Canada	Markforged Onyx One	Onyx (Proprietary)	Not specified	Framework for clinical commissioning of 3D-printed support devices
Zhu et al. [65]	2015	Holland/ USA	Replicator 2X	PLA	OpenSCAD	Fabricating cerrobend grids

Lee et al. [93]	2016	Korea/USA	Makerbot Z18	Not specified	Not specified	Depth-sensing technique on 3D-printing compensator for total body irradiation patient measurement and treatment planning
Fuller et al. [67]	2017	USA	Form 2	Not specified	Meshmixer, PreForm	3D-printer oral stent for H&N radiotherapy from routine diagnostic imaging
Park et al. [70]	2017	Korea	ProJet 3510 SD	VisiJet M3 Crystal	Meshmixer	Total body irradiation with a compensator fabricated using a 3D optical scanner and a 3D-printer
Dancewicz et al. [94]	2017	Australia	3D Touch, Replicator 2, Taz 5	ABS, PLA, woodfill, bronzefill, coperfill	Sketchup	Radiological properties of 3D-printed materials in kV and MV photon beams
Craft et al. [23]	2018	USA	Gigabot 3.0	PLA, NinjaFlax, ABS, Cheetah	Not specified	Density uncertainty in 3D-printing
Zhao et al. [80]	2017	Canada	MakerBot Z18, LulzBot Taz 5	PLA, NinjaFlex	In-house	Review of clinical applications of 3D-printing in radiotherapy

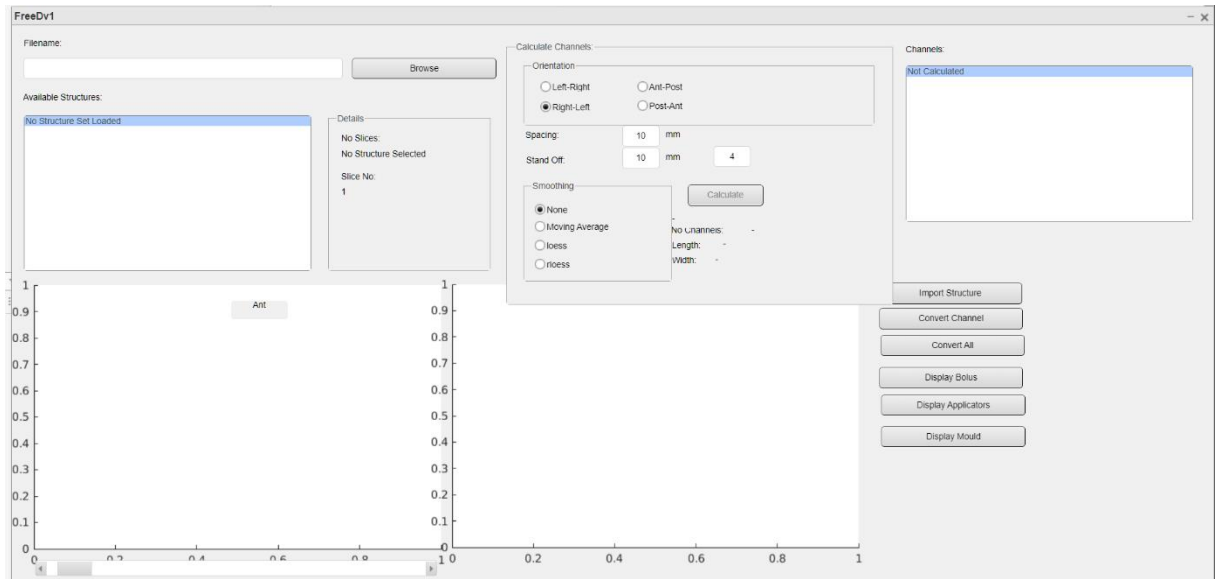
Pugh et al. [21]	2017	New Zealand/ UK	n/a	n/a	n/a	Literature review of 3D-printing within radiotherapy to improve bolus conformity
Sethi et al. [12]	2016	USA	Fortus 400mc	PC-ISO	Autodesk	Clinical applications of custom-made vaginal cylinders
Cunha et al. [11]	2015	USA	Fortus 400mc	ABS/PC-ISO	Not specified	Evaluation of PC-ISO for customised gynaecological brachytherapy applicators
Lindegaard et al. [56]	2016	Denmark	Projet 3510 SD	Visijet M3 Crystal	MATLAB, Solidworks	Individualised 3D-printed vaginal template for MRI guided brachytherapy
Arenas et al. [58]	2017	Spain	BCN3D Sigma	Not specified	Meshmixer	Individualised 3D scanning and printing for skin brachytherapy: a financial study
Ji et al. [62]	2017	China	Not specified	Photo-curable resins	Magics	Dosimetric verification of a 3D-printed template guided brachytherapy
Sim et al. [95]	2016	Australia	Stratasys Objet Connex 500	MED610	Autodesk Inventor	3D-printed insert for I-125 ROPES eye plaque therapy
Sekii et al. [57]	2018	Japan	DMM.com Base	PC-ABS	Fusion 360	Inversely designed 3D-printed personalised templates for interstitial brachytherapy for vaginal tumours

Ricotti et al. [51]	2016	Italy	Hamlet 3DX100	ABS	TinkerCAD, Peak-3D	Dosimetric evaluation of 3D-printed applicators for HDR brachytherapy
Poulin et al. [59]	2015	Canada/ USA	MakerWare, Replicator 2X	PLA	Solidworks 2012	Personalised 3D-printing for breast brachytherapy
Huang et al. [61]	2016	China	Not specified	Not specified	Not specified	Accuracy evaluation of 3D-printed individual template for needle guidance in prostate brachytherapy
Jones et al. [15]	2017	UK	Stratasys Objet 500 Connex 1	TangoPlus FullCure930	MATLAB, Mimics Medical. 3-matic	3D-printed superficial applicators for HDR skin brachytherapy
Li et al. [7]	2017	China	3510 SD	ABS	Mimics	Interstitial brachytherapy using 3D-printed vaginal templates
Jiang et al. [63]	2018	China	Not specified	Not specified	Not specified	Side effects of CT-guided brachytherapy for H&N tumours assisted by 3D-printed templates
Harris et al. [64]	2015	Australia	3D Touch	ABS	MATLAB, Meshlab	Patient specific brachytherapy mould design using a low-cost 3D-printer
Madamesila et al. [25]	2016	Canada	ORION Delta 3D	HIPS	Repetier	Characterizing 3D-printing in the fabrication of variable density phantoms for QA phantoms in radiotherapy

Leary et al. [26]	2015	Australia	Not Specified	Not Specified	Not Specified	3D-printed custom radiotherapy phantoms
Kim et al. [96]	2017	Korea	Object Connex, Titan 1	Acrylic polymer	Meshmixer, SolidWorks	Characterisation of 3D-printed techniques for patient specific QA spine-shaped phantoms for stereotactic radiotherapy
Quinones et al. [27]	2018	Spain	Prusa i3 MK2	PLA	Not specified	Open-source 3D-printed lung phantom for radiotherapy QA
Jung et al. [97]	2015	USA	3D Edison	PLA	Not specified	Accuracy of CyberKnife tumour tracking using a 3D-printed patient-specific lung phantom
Zavan et al. [30]	2018	Canada/ USA	ORION Delta 3D	Polystyrene	Not specified	Verification of Acuros XB dose algorithm using 3D-printed low-density phantoms
Craft et al. [35]	2017	USA	Gigabot 2.0	PLA	Osirix, netfabb, MeshLab, Simplify3D	Preparation and fabrication of a full-scale 3D-printed patient-specific radiotherapy phantom
Kamomae et al. [9]	2017	Japan	FDM-200W	PLA	Osirix, Shade3D	3D-printed patient-specific phantom for artificial in-vivo dosimetry in radiotherapy QA

Mayer et al. [28]	2015	USA	Stratasys Objet500 Connex3	TangoPlus, Vero White	Mimics	3D-printer generated thorax phantom with mobile tumour for radiation dosimetry
Woods et al. [31]	2018	USA	BCN3D Sigma	Not specified	Not specified	Quality assurance for a six degrees-of-freedom table using a 3D-printed phantom
Ehler et al. [33]	2014	USA	Makerbot Replicator 2x	ABS	3DSlicer	Patient-specific 3D-printed phantoms for IMRT QA
Oh et al. [36]	2017	Korea	Finebot Z420	PLA	Not specified	Variable density 3D-printed phantoms for QA in radiotherapy
Yea et al. [34]	2017	Korea	Stratasys Dimension 1200	ABSplus	3DSlicer	3D-printed anthropomorphic patient-specific head phantoms for IMRT QA
Oh et al. [98]	2017	Korea	Finebot Z420	PLA	Not specified	Development of patient specific phantoms for verification of stereotactic body radiotherapy

Appendix 5 – Overview of custom MATLAB script



FreeDv1.m
Main interface/GUI screen
Author: James Burnley

CoordsToTube.m
Converts a series of co-ordinates to cylindrical tubes and saves as .stl file type
Author: James Burnley

FreeD (Version 1)
Custom MATLAB script used to analyse DICOM structures and compute catheter trajectories for surface brachytherapy. Exports individual trajectories as tubes in .stl file format for 3D-printing.
Source code may be available on request from the author and at the risk of the user. Not intended for use as a medical device.
James Burnley, August 2018

Contact: jburnley@nhs.net

surf2stl function
Write STL file from surface data
Version: 1.0.0.0
Author: Bill McDonald
Source:
<https://uk.mathworks.com/matlab-central/fileexchange/4512-surf2stl>

tubeplot function
Constructs a tube along any 3D curve.
Version: 1.0.0.0
Author: Janus H. Wesenberg
Source:
<https://uk.mathworks.com/matlab-central/fileexchange/5562-tubeplot>